STUDY ON THE EFFECTS OF VARIOUS DISINTEGRANTS ON AMOXICILLIN TRIHYDRATE DISPERSIBLE TABLETS

Dissertation

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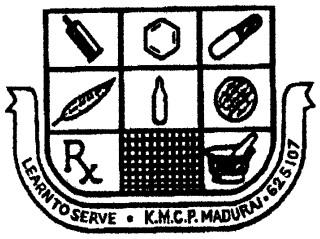

DEPARTMENT OF PHARMACEUTICS

K.M.COLLEGE OF PHARMACY

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APRIL – 2012

CERTIFICATE

This is to certify that the dissertation entitled "**STUDY ON THE EFFECTS OF VARIOUS DISINTEGRANTS ON AMOXICILLIN TRIHYDRATE DISPERSIBLEE TABLETS**" submitted by **Mr**. **MATHEW EBIN P SOVICHAN** to The Tamilnadu Dr.M.G.R.Medical University, Chennai, in partial fulfillment for the award of Master of Pharmacy in Pharmaceutics at K.M. College of Pharmacy, Madurai, is a bonafide work carried out by him under my guidance and supervision during the academic year **2011-2012.**

PRINCIPAL & GUIDE

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DEDICATED TO MY

PARENTS

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Mathew Ebin P Sovichan

ABBREVATIONS

L	Litre
ml	millilitre
hr	hour
min	minute
sec	second
gm	gram
mg	milligram
ADME	Absorption, Distribution, Metabolism & Excretion
nm	nanometre
mm	millimetre
µm	micrometre
w/w	weight/weight
w/v	weight/volume
µg/ml	microgram/milllilitre
g/cc	gram/cubiccentimetre
m^2/g	Square metre/ gram
#	mesh size
^0C	Degree celsius
rpm	Rotation per minute
%	Percentage
ICH	International conference on harmonization
USP	United states Pharmacopoeia

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1. INTRODUCTION

An ideal drug therapy was based on relating pharmacological response to the dose administered. Poor correlation between the dose administered and pharmacological responses will be resulted because of the decreased absorption rate or poor dose rate. Deviation in the plasma drug concentration also will result due to the formulation factors and elimination characteristics resulting in toxicity. To reduce these problems an appropriate dosage regimen should be selected, which would attain the plasma concentration immediately after the administration and it should also kept the drug concentration below the maximum safe concentration. This possible by the administration of conventional dosage form in a particular dose at a particular frequency and should be convenient to patient for the administration.[1]

Drugs may be administered in various routes in a variety of dosage forms. The most important and popular route of administration is oral route. Because of its popularity and convenience almost every new drug that is newly developed will be tested for its effectiveness as an oral dosage form during its initial stages of formulations.

Dosage forms that are administered through the oral routes are syrups, suspension, elixirs, capsules and tablets. Among these tablets and capsules are the most popular and convenient oral dosage formulations. Tablets offer best protection of the drugs against light, temperature, humidity, oxygen and moisture. Thus it will provide increase stability to the drug and the tablets are tampering proof dosage form.

1.1. Oral Drug Delivery System

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs via various pharmaceutical products of different dosage forms.

All the pharmaceutical products formulated for systemic delivery via the oral route of administration, irrespective of the mode of delivery (Immediate, Sustained or Controlled release) and the design of dosage forms (either solid, dispersion, or liquid), must be developed within the intrinsic characteristics of GI physiology.[2] As shown in the table no.1

The most sophisticated delivery system, the greater is the complexity of these various disciplines involved in the design and optimization of the system. In any case, the scientific framework required for the successful development of an oral drug delivery system consists of a basic understanding of the following three aspects:

1) The anatomic and physiologic characteristics of the gastrointestinal tract. As shown in below table.
2) Physicochemical, pharmacokinetic and pharmacodynamic characteristics of the drug.
3) Physicomechanical characteristics and the drug delivery mode of the dosage form to be designed.

Anatomic and physiologic characteristics of the gastrointestinal tract

Table No.1

Region	Surface Area (m2)	pH of The Region	Transit Time	
			Fluid	Solid
GIT	200	1-8	-	-
Stomach	0.1-0.2	1-3.5	50 min.	8 hrs.
Small intestine	4500	5-7.5	2-6 hrs.	4-9 hrs.
Large intestine	0.5-0.1	6.8	2-6 hrs.	1hrs to3days

1.2. TABLETS[3]

Tablets are defined as solid pharmaceutical dosage forms containing medicament with or without suitable excipients and prepared either by compressing or moulding.

Advantages of tablet

- Unit dosage form and dose precision
- Low cost
- Special release profile
- Better stability
- Better patient compliance

Disadvantages of tablets

- Some drugs resist compression in to dense compacts.
- Drug with low dissolution, poor wetting, optimum absorption of drug from gastro intestinal tract will cause difficulty in formulating tablets
- Bitter tasting drug, drugs with objectionable odour or drug sensitive to moisture are difficult to formulate as tablets

1.3. Manufacturing of tablets

Granulation[3,51]

Granulation is the process of collecting particles together by creating bonds between them. Bonds are formed by compression or by using binding agent. Granulation process is the most important process in the tablet making steps; a tablet with good characteristic is not made in the tablet press but in granulation process. Joining the particle with in a granulation process will improve flow and compression characteristic, reduce segregation, improve uniformity and eliminate excessive amount of fine powders. A fine granulation process will yield a reduced defect, increased yield and reduced time in tablet production. The best course of action is to ensure each tablet containing same amount of the active drug is by mixing the active thoroughly with some or most of the active ingredients and then granulate the blend. Each granule should contain small amount of active ingredient and other ingredients in evenly amount. If the active ingredient is high in quantity it should be granulated with itself if they have appropriate compressibility properties. The granulation process is the most important process in the tablet manufacturing process, three basic techniques are used to prepare granules for the compression of the tablets they are

- *Direct compression*
- *Wet granulation*
- *Dry granulation*

Direct compression

In this process the drug materials are compressed directly, the compression of a single substance does not produce an acceptable disintegration. For disintegration problem other substance are added to overcome. The flow property and the compressibility index of the excipients added along with the drug also will be an important factor in this type of compression method. Direct compression has some advantage of low labor input, a dry process fewest processing step and also have limitations like interaction of the diluent with drug substance.

***Wet granulation*[51]**

When the drug substance and the diluent are fluffy, fine it will not stay in the blend causing problem in mixing and filling in the die cavity resulting in weight variation etc. the wet granulation is the process of addition of granulating agent usually liquid solution in to the powder which will help in the formation of bonds between the powder forming granules. The liquid solution can be an aqueous solution or non-aqueous solution depending up on the nature of the powder. The granules will be dried on a hot air oven to particular moisture content over dried granules will break up easily and producing small particles called fines. Fines do not flow well in to the die cavity and can result in tableting problems.

***Dry granulation*[51]**

Dry granulation process is used to form granules without using a liquid solution because the product using will be sensitive to moisture an heat. Forming granules without liquid needs the powder to be compacting and densifying by the process called slugging. Slugging is done by the roller compactor to form a compacted powder and it is finally passed through the mill and blend before compression.

Advantage of direct compression

- Economical, fewer manufacturing steps, less processing time and low labor cost.
- No moisture, heat and high compaction pressure.
- Important effects on tablet disintegration.

1.4. Classification of tablets[3]

A. Oral tablets for ingestion

- Compressed tablets
- Multiple compressed tablets
- Compression-coated tablets
- Repeat-action tablets
- Delayed-action and enteric-coated tablets
- Sugar and chocolate –coated tablets
- Film coated tablets
- Chewable tablets
- Layered tablets

B. Tablets used in the oral cavity

- Buccal tablets
- Sublingual tablets
- Troches and lozenges
- Dental cones

C. Tablets administered by other routes

- Implantation tablets
- Vaginal tablets

D. Tablets used to prepare solutions

- Effervescent tablets
- Dispersible tablets
- Hypodermic tablets
- Tablet triturates

1.5. Dispersible tablets[24]

Despite the increasing interest in controlled release drug delivery systems the most common tablets that are intended to be swallowed whole and to disintegrate and release their medicament rapidly in the gastro intestinal tract still remains the dosage form of choice. Dispersible tablets are uncoated or film-coated tablets intended to be dispersed in water before administration giving a homogeneous dispersion. Hence proper choice of disintegrants and its consistency of performance are of critical importance to the formulation development of such tablets. The administrations of the drugs to the elderly patients have become a major barrier in drug therapy, mainly due to the difficulty in swallowing disability. These tablets are dispersed in the water before administration. Dispersible tablets are well administered for the pediatric, dysphasic patients, mentally ill, unco-operative and nauseated patients, those with conditions of motion sickness, sudden episodes of allergic attack or coughing. The dispersible tablets are preferred dosage form of WHO for the pediatric and elderly patients. The WHO specify dispersible tablet particularly suitable for children from 5 kg to 35 kg. The tablet disintegrates in to the water in to a pleasant tasting suspension.[56] Dispersible tablets are manufactured mainly by direct compression, wet granulation and dry granulation. The dispersible tablet should disperse in the water with in 3 min to produce a uniform dispersion. Pharmacopoeia specify a dispersion test exclusively for dispersibility tablet, 2 tablets placed in 100 ml of water and stirred until completely dispersed. A smooth dispersion is produced, which passes through a sieve screen with a nominal mesh aperture of 710 µm. Due to the administration of the drug in the dispersed from the area of absorption of the drug will be high when considering the conventional tablets. Drug which shows instability in the water can be formulated. Drug which having unacceptable taste can be masked in dispersible tablet. Compression of the drug substance alone in to a tablet wouldn't produce acceptable disintegration time. So to increase the disintegration time a disintegrating agent are added to promote the breakup of the tablet in to small fragments in the aqueous environment and their by increasing the available surface area and absorption of the drug. There are three method to in cooperate the disintegration agent to the tablet they are*; a. Internal addition b. External addition c. Internal and External*

addition.[49] In a direct compression process, drug is blended with a variety of excipients, subsequently lubricated and directly compressed into a tablet. Disintegrants used in this type of formulation, simply has to break the tablet apart to expose the drug substance for dissolution.

Advantages of dispersible tablet

- They are easy to swallow, so easy administration for elderly and childrens.
- Quicker onset of action.
- The tablet can also be divided.
- The bitter taste of the active substance can be masked in advance.
- Improved tablet performance
- Applicability across a wide range of drugs with different physicochemical properties.

Disadvantages of dispersible tablet

- These tablets contain high concentration of disintegrants that tend to weaken the tablet structure.
- Hygroscopic properties of these tablets are high.
- Stability will be altered with atmospheric condition.
- Inaccurate dosing.
- Dispersible tablets should need a proper packing for proper stabilization and safety of the products.

1.6. Disintegrating agent[25,50,37,38]

A drug given in an orally administered tablet must undergo dissolution before it can be absorb and transported in to the systemic circulation. For many drugs dissolution must be preceded by disintegration of tablet matrix. For tablet dissolution it is necessary to overcome cohesive strength introduced in to the mass by compression. Therefore usual practice of incorporating the *disintegrating agent* will overcome this. Disintegration is frequently considered a prerequisite for drug

dissolution, it is no matter assures that drug will dissolved and hence have the potential for satisfactory bioavailability.[50] The development of fast dispersible tablet using super disintegrants has become popular for various reasons. For tablet containing sparingly water soluble drugs, the start of dissolution is often delayed by the poor wettability of tablet or slow liquid penetration into tablet matrix. This will result in increase in the disintegration time and retards the drug release. This can be overcome by the addition of super disintegrants. The superdisintegrants such as Croscarmellose sodium, sodium starch glycolate and Crospovidone are now frequently used in the formulation to improve the rate and extent of tablet disintegration thereby increasing the rate of drug dissolution.[48] The total porosity and pore mean diameter decrease, when applied pressure increased and consequently the disintegration time increase. Under certain condition the superdisintegrants makes enough pressure pores of the tablets as to produce an efficient disintegration. Although the rate of capillary penetration in tablets of narrower pore size distribution, larger parts of pore structure participate in liquid uptake.

There are three methods of incorporating disintegrating agents in to tablet: A. Internal addition (intragranular) B. External addition (Extragranular) C. Partly Internal and External[49]. In a direct compression process drug is blend with a variety of excipients, subsequently lubricated and directly compressed in to a tablet.

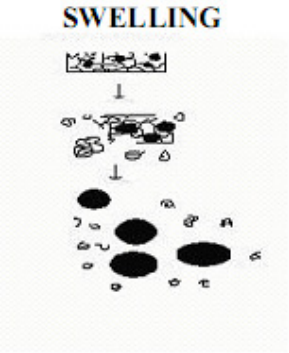
There are mainly four main mechanism of action for the disintegrants they are,[29,48,49]

1. Swelling
2. Porosity and capillary action (wicking)
3. Deformation
4. Due to disintegrating particle/particle repulsive forces

1. **Swelling**

General mechanism of action for tablet disintegration is swelling. Swelling is the mechanism in which the disintegrating effect is by swelling in contact with water the adhesiveness of other excipient in a tablet will be overcome causing the tablet to disintegrate.

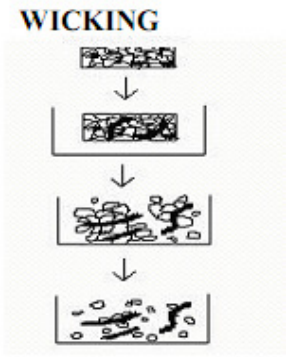
Example: Starch and Modified starch (Sodium starch glycolate).



2. ***Porosity and Capillary Action (Wicking)***

Disintegration by capillary force is the main step in disintegration. When the tablet is put in a suitable medium, the medium will drawn up or "wicked" in to these pathways through the capillary action and causes the breakup of the interparticulate bond between the particle.The good disintegrating property of the tablet will be depend up on the wetting property of the ingredients. The major wetting property was brought to the excellent wicking property of the disintegrants.[29] The water uptake of the tablet will be depends up on the drug and excipients and on tablet conditions. These type of disintegrants wil maintain a low interfacial tension and high porous structure.

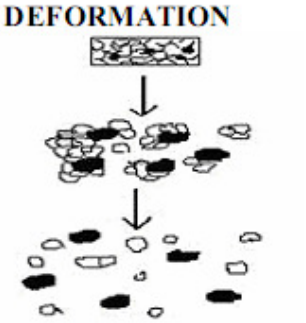
Example: Crospovidone.



3. *Deformation*

During tablet compression, disintegrated particle get deformed and these deformed particles get in to normal form when they came in contact with aqueous medium.[48] Swelling capacity of the starch was improved when the granules are extensively deformed during compression. Increased in the size of the starch granules will thus cause the breakup of the interparticulate bond in tablet. Starch is granules are widely studied for this property.

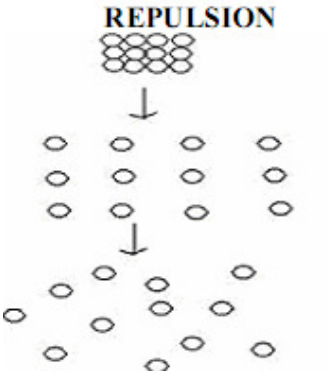
Example: Starch Maize.



4. *Due to disintegrating particle/particle repulsive forces*

This explains the disintegration of tablet made with 'nonswellable' disintegrants. Guyot-Hermann has proposed a particle repulsion theory based on the observation that nonswelling particles also causes disintegration of the tablet. The repulsive force between the particles are the main mechanism of action of

disintegrants act by this mechanism, at lower concentration it will cause good disintegrating property and improved compressibility for the tablets.
Example: Gellan gum



Wicking and swelling were found to be the primary mechanism of action for tablet disintegration, while other mechanisms such as deformation and particle repulsion theory etc may play a role in particulate cases of tablet disintegration

Advantage of Superdisintegrants[49]

- Remarkable tendency on wetting causing rapid disintegration.
- No lump formation on disintegration
- Compatible with commonly used therapeutics agents and excipients.
- Work equally effective in hydrophilic and hydrophobic formulations
- Provides good mechanical strength to the tablet facilitating easy packing and transportation.
- Does not stick to the punches and dyes.

Disadvantages of use of disintegrants in direct compression formulation[49]

- High concentration needed for optimum disintegration efficiency
- Poor disintegration
- Susceptibility to high compression forces which decrease the efficiency
- Poor compression properties
- Decreased disintegrating efficiency in hydrophobic formulations

1.7. Drug market value and resistance.

Amoxicillin[21,17,39,40,41]

Amoxicillin is a semi synthetic antibiotic, an analogue of ampicillin, with a broad spectrum of bactericidal activity against many gram positive and gram negative organism. The main mechanism of action is amoxicillin binds to penicillin binding protein located inside the bacterial cell wall. Pencillins acrylates the pencillin sensitive transpeptidase C-terminal domain by opening the lactum ring. This inactivation of the enzyme prevents the formation of a cross link of two linear peptidoglycan strands, inhibiting the third and last stage of bacterial cell wall synthesis. The amoxicillin is used as amoxicillin trihydrate in oral preparation.[17] Amoxicillin trihydrate is likely white or almost white crystalline powder and it is well absorbed when given orally, with a bioavailability that appears to be much higher than excepted based on its physicochemical and biopharmaceutical properties and the pH partition theory. The trihydrate form is slightly soluble in water and its stability in the solid state is possibly related to the effect of the water content and hygroscopic behavior. Because of its poor solubility amoxicillin trihydrate can be considered as a drug candidate which may give rise to dissolution related bioavailability problem.

Market value of the drug[52,31]

In spite of availability of many new generation antibiotics- Amoxicillin is still very popular. Its one of the most common antibiotics prescribed for children. Amoxicillin stands 5th in 2008 top generic drugs by total prescriptions. Export of amoxicillin has been growing for last 6 years at very healthy rate. Market Size and Growth Overseas market of amoxicillin for 2008-09 is estimated to be Rs. 547 crores (USD 118 million). Total sale of all amoxicillin formulations at the end of March 2004 was Rs. 150 crores (USD 33 million). Since then, the market has been growing at a very healthy rate of 24% CAGR (Compounded Annual Growth Rate) 10 countries account for 49% export of Amoxicillin. South Africa, Nigeria, Myanmar, Sri Lanka and Netherlands are top 5 export markets of Amoxicillin, as per analysis of shipment

records collected from 18 major seaports, airports and dryports. South Africa emerges as the largest market, accounting for 11.19% market share (2008-09) by value. Nigeria, Myanmar and Sri Lanka follows in quick succession. Africa and Middle east are the largest regional markets**.**

Drug resistance[53,54]

The amoxicillin have been widely used in the outpatient arena for the treatment of community acquired respiratory tract and mild to moderate infections, due to the continues use of this drugs results in the resistance of the many organism to the amoxicillin like antibiotics.[36] In most Western countries, microbiological testing may be unnecessary in acute uncomplicated urinary tract infections, except for surveillance purposes because in most cases urine culture and susceptibility testing cost more than the antibiotic treatment itself. The Infectious Diseases Society of America (IDSA) guidelines currently recommend empirically treating acute, uncomplicated bacterial cystitis in healthy adult, nonpregnant females with a 3-day course of double-strength trimethoprim-sulfamethoxazole in settings where the prevalence of sulfamethoxazole resistance is 10-20%.[37] Alternative therapies for uncomplicated UTI include a fluoroquinolone, nitrofurantoin or fosfomycin, wherever sulfamethoxazole resistance is 10-20% .However, these guidelines may not be applicable in other countries such as India. The resistance pattern of community acquired uropathogens has not been extensively studied in the Indian subcontinent. This study was planned to identify the most common pathogens associated with community acquired urinary tract infections in India and to determine their antibiotic sensitivities. This epidemiological data is essential to help formulate guidelines on empirical antibiotic treatment of uncomplicated community acquired urinary tract infections in India. Most of the individual in India have acquired severe resistance to amoxicillin like antibiotics, this result in forcing the use of new or increased drug therapy.

LITERATURE REVIEW

K.F.M.Pasqualoto[26] et al., (2004), Amoxicillin tablets were developed by direct compression using a factorial design. Eight different formulation were carried out and they were analyzed considering three levels:the type of microcrystalline cellulose, the presence or absence of spray-dried lactose, and the presence or absence of the super disintegrants agent, Croscarmellose sodium. Average weight, thickness and diameter, hardness,friability, amoxicillin concentration, disintegration time and dissolution profile were the parameters used for the tablets evaluation.

Andries F.Marais[27] et al., (2003) formulated directly compressed amoxicillin-Avicel,Ac-Di-Sol. The fast disintegration of the tablet with in one to two minute is a prerequisite for improving the dissolution of furosemide. Ac-Di-Sol was and efficient disintegrant for furosemide tablet at low concentration.

Sagar Bhise[28] et al., (2009) developed amoxicillin using solid dispersion (SD) with crospovidone, croscarmellose sodium and sodium starch glycolate by using kneading technique. it was concluded that the solubility and dissolution of model drug furosemide was increased due to solid deposition of drug upon surface of hydrophilic and strongly swelling superdisintegrants which enhanced the wettability and dispersibility of poorly water soluble drug furosemide which is prerequisite step for poorly water soluble drug.

Priyanka Nagar[29] et al., (2011) developed orally disintegrating tablet (ODT) of amoxicillin trihydrate which rapidly disintegrate & dissolve in saliva and then easily swallowed without need of water which is a major benefit over conventional dosage form. In addition, patients suffering from dysphasia, motion sickness, repeated emesis and mental disorders prefer such preparation because they cannot swallow large quantity of water. Further, drugs exhibiting satisfactory absorption from the oral mucosa or intended for immediate pharmacological action can be advantageously formulated in such type of dosage form.

Admo Fini[30] et al., (2008) selected tablet formulation, containing 26% amoxicillin and 5% crospovidone, disintegrates before the amoxycillin starts to swell. These tablets disperse in water within 40 s and show a crushing strength of 95 N. To develop an orodispersible tablet, a rotatable central composite design was applied to predict the effects of the quantitative factors mannitol and crospovidone as well as compression force on the characteristics of the tablet. Special emphasis was paid to the development of a wetting test, replacing the normal disintegration method. An optimum tablet formulation, containing 34% mannitol and 13% crospovidone, provides a short wetting time of 17 second and a sufficient crushing strength of 40 N. Fast dispersible tablets with acceptable hardness and desirable taste could be prepared within the optimum region.

Mauro Cavinato[31] et al., (2011) studied three common active pharmaceutical ingredients (amoxicillin, caffeine and acetylsalicylic acid) were used within the initial formulation. Drug load was 50% (on weight basis.Influences of drug particle properties (e.g. particle size and shape, hygroscopicity) on the granule growth behaviour were evaluated. Resistance of the wet mass to mixing was furthermore measured using the impeller torque monitoring technique. The observed differences in the granule growth behaviour as well as the discrepancies between the actual and the ideal drug content in the final granules have been interpreted in terms of related to torque measurements. On the other hand where penetration time was lower (e.g. acetylsalicylic acid-based formulations), the growth was much faster but uniformity content problem arose because of the onset of crushing and layering phenomena.

Xiaorong He[32] et al., (2008) investigated amoxicillin trihydrate and croscarmellose sodium (Ac-Di-Sol) in a direct compression formulation containing a poorly water soluble drug (albumin tanate) at high dosage investigated. An experimental design with two variables,applied pressure and concentration of Ac-Di-Sol, allowed the evaluation of microstructural, mechanical and disintegration properties of the tablets. Tablet properties evaluated were affected by both variables, while compression parameters were essentially dependent on applied pressure. The shortest disintegration time was found for mixtures more prone to plastic deformation and densification at same level of applied pressure. These mixtures also revealed a finer pore structure. The different rearrangement of disintegrant particles in powder mixture is suggested

to explain the dominant effect of the disintegrant bonding mechanism presented at a given mixture composition.

Naz Haasan Huda[33] et al., (2009) studied Amoxicillin Trihydrate capsules in water for 60 minutes using USP reference dissolution apparatus. All, except two national brands ; complied with the USP *in vitro* dissolution specification for drug release (not less than 80% of the labelled amount of amoxicillin trihydrate should be dissolved in 60 minutes). Drug releases from those two brands were 75% and 67% respectively within the specified time period.

A.N.Zaid[34] et al., (2010) evaluated two capsules Amoxicillin 500mg and one Amoxicillin 100mg tablet have similar bioequivalence parameter. For this purpose a randomized, two way, cross over, bioequivalence study, was performed in 24 healthy male, volunteers, divided in to two groups of 12 subjects each. One group was treated with standard and other with amoxicillin tablet. Blood samples were collected at fixed intervals and pharmacokinetic parameters were determined.

Pirrre Leroy[35] et al., (1992) developed HPLC method and microbiological assay developed for measuring amoxicillin in calves plasma were used in pharmacokinetic studies of antibiotics following IM administration of the test compound. The samples were assayed by the two methods. The HPLC techniques included protein precipitation of plasma samples with trichloroacetic acids, isocratic elution on a reversed phase column. The microbiological method is by agar gel diffusion method. Both method show full selectivity with regard to endogenous compounds and a co-administrated antibiotic.

Theerasak Rojanarata[36] et al., (2010) developed method for amoxicillin in pharmaceutical preparation was assayed by two enzymatic reaction. In this work the assay condition were studied and optimized and the method was validated. Good accuracy and precision were obtained when the method was tested with amoxicillin capsule and powder for oral suspension. No interference from common excipients in the formulations or degradation products was observed, this proposed assay was an ideal green analytical method suitable for the quality control of amoxicillin for the pharmaceuticals.

Pei-Yi Li[37] et al., (2007) effect of amoxicillin on the cellular DNA integrity was studies, in which amoxicillin was added to the human or hamster cells in culture, and the DNA lesions induced by the drug were assessed by a comet assay with nuclear extract incubation. Amoxicillin rapidly induced DNA lesions in human cells. The level of DNA lesions attained a maximum at about 1 h, and then declined steadily and reached almost the basal level at 6 h following the drug treatment. Similar induction pattern of DNA lesions was found with amoxicillin-related antibiotics such as ampicillin but not with the unrelated antibiotics such as kanamycin. Repair kinetics of the cells were treated with amoxicillin for only 1 h and continued culture in the absence of the drug for a certain period of time before subsequent analysis. Repair of the amoxicillin-induced DNA lesions was essentially completed within 4 h.Amoxicillin induced intracellular reactive oxygen species (ROS) at the tempo similar to that of DNA lesions induction.

Badraddin Mohammed Al-Hadiya[38] et al., (2011) amoxicillin trihydrate suspension marketed as Hymox suspension as compared with the reference product, Amoxil suspension to healthy adult male subject under fasting conditions, for the purpose of registration, approval and marketing stage. The subjects received Hymox suspension, as a test product and Amoxil suspension as a reference in a single-dose, randomized, two way crossover design fashion on 2 treatment days, after an overnight fast of at least 10 hours, with a washout period of 7 days. Blood samples were collected at prespecified times over a period of 30 hours after administration. The bioanlaysis of clinical plasma samples was accomplished by an HPLC method, it found that the two formulations were considered to be bioequivalent.

Giacomo Fontana[39] et al., (2001) amoxicillin was loaded with Polyethyleneglycol (PEG)-coated polyethylcyanoacrylate (PECA) nanoparticles influence of the PEG coating on the particle size, zeta potential, drug release rate and phagocytic uptake by murine macrophages. Phagocytosis was evaluated by incubating amoxicillin loaded PECA nanoparticles with murine macrophages and determining the amount of phagocytized nanoparticles by dosing the amoxicillin present inside the macrophages of urease, the mucoadhesive properties of polyalkylcyanoacrylate nanoparticles and

the activity of the amoxicillin versus *Helicobacter pylori*, colloidal drug selivery system developed was suitable for the treatment against the *Helicobacter pylori.*

K. Prakash[40] et al., (2008) amoxicillin trihydrate in pharmaceutical bulk and tablet dosage was determined with spectroscopical method form using citro phosphate buffer pH 7.2. The system obeys Lambert-Beer's law at 231 nm in the concentration range 2.5-50 µg/m. This methods have been successfully applied to the analysis of the bulk drug and its tablet dosage form. The methods have been statistically evaluated and were found to be precise and accurate.

Zhepeng Liu[41] et al., (2005) amoxicillin mucoadhesive microspheres were prepared using ethylcellulose as matrix and carbopol as mucoadhesive polymer for the potential use of treating gastric and duodenal ulcers. In vitro release test showed that amoxicillin released faster in pH 1.0 hydrochloric acid (HCl) than in pH 7.8 phosphate buffer. Amoxicillin was not stable in an acidic surrounding. It was also found that amoxicillin entrapped within the microspheres could keep stable. In vitro and in vivo mucoadhesive tests showed that amoxicillin microsphere adhered more strongly to gastric mucous layer than non-adhesive amoxicillin microspheres could retain in gastrointestinal tract for an extended period of time. Studies showed that amoxicillin microsphere had a better clearance effect than amoxicillin powder did. The prolonged gastrointestinal residence time and enhanced amoxicillin stability resulting from the mucoadhesive microspheres of amoxicillin might make contribution to H. pylori clearance.

Vinay Pandit[42] et al., (2010) amoxycillin trihydrate was prepared as floating tablets. The formulations were prepared as matrix tablets in the form non effervescent tablets. Various grades of hydroxy propyl methyl cellulose were used to achieve controlled release of the drug. Granules were prepared by wet granulation technique and compressed into tablets. The prepared tablets were evaluated for weight variation, hardness, friability, drug content, buoyancy and in vitro dissolution studies. Optimized formulation of amoxicillin was found to have increased gastric residence prolonging the release of drug with 85% of drug release in 6 hours by diffusion. The mechanism of drug release was found to be diffusion and followed combination of zero order and first order kinetics.

N.Venkateswaramurthy[43] et al., (2010) amoxicillin mucoadhesive microspheres, which have the ability to reside in the gastrointestinal tract for an extended period, were prepared. Amoxicillin microspheres were prepared by using Eudragit RL100 as matrix and carbopol 974P as mucoadhesive polymer. The microspheres were prepared by emulsion solvent evaporation technique. The prepared microspheres were evaluated with respect to the particle size, production yield, encapsulation efficiency, shape and surface properties, mucoadhesive property, *invitro* drug release and suitability for anti *Helicobactor pylori* effect. In conclusion, mucoadhesive microspheres of amoxicillin prepared in this study could stay in the gastrointestinal tract for a longer period of time. Which indicate a potential use of mucoadhesive microspheres of amoxicillin in treating *H. pylori* infection.

Catherine Bisson-Boutelliez[44] et al., (2010) amoxicillin and β cyclodextrin complexes were prpepared by two methods and then the interaction were determined. The extent of complexation in solution has been evaluated by high-performance liquid chromatography, nuclear magnetic resonance and 2D rotating-frame Overhauser enhancement spectroscopy. Mass changes calorimetric effects, and mass spectrometry were determined on the same sample under identical conditions using the Skimmer coupling system. Skimmer and infrared spectroscopy were used to characterize the solid state of the binary system. Complexation of AMOX with β-CD was proven by FT-IR, NMR, DSC, and HPLC. The 2D ROESY spectra did not show any dipolar proton interaction of the amoxicillin with cyclodextrin. The stability constant for amoxicillin with β-CD was determined.

AidongWen[45] et al., (2008) amoxicillin were determined simultaneously ambroxol in human plasma using clenbuterol as internal standard (IS). The plasma samples were subjected to a simple protein precipitation with methanol. Separation was achieved on a Lichrospher C18 column using methanol and water as a mobile phase by gradient elution at a flow rate of 1.0 mL/min. Detection was performed using electrospray ionization in positive ion multiple reaction monitoring (MRM) mode by monitoring the ion transitions. Calibration curves were linear in the concentration range of 5–20,000 ng/mL for amoxicillin, and 1–200 ng/mL for ambroxol, with the intra- and inter-run.

Kiron S[46] et al., (2011) amoxicillin tablets of different brands were selected for this study as amoxicillin molecule is highly sensitive to temperature and humidity. Adequate quantities of samples were procured from hospital and community pharmacies located in different regions of Kerala. Samples collected from different time intervals were suitably coded and analyzed for all the listed parameters. It was observed that, there were seasonal fluctuations in the Mean Kinetic Temperature and Mean Kinetic Humidity in the various regions of Kerala. The study data show that percentage strength of amoxicillin was least in samples collected from Cochin compared with those collected from other region of kerala. Mean kinetic humidity was more in coastal area, which may have accelerated the degradation of amoxicillin in samples from Cochin. Microbiological data showed significant reduction in zone of inhibition for samples collected from Cochin in comparison with other regions.

Sayaka Nakanishi[47] et al., (2011) studied solid dispersion powder of indomethacin with Crospovidone shows useful characteristics for manufacturing dosage form. Four types commercial Crospovidone, polyplasdone XL used as the initial carrier. Polyplasdone Xl 10 and colidone were compared. The limit of the indomethacin-crospovidone weight ratio with which a soild dispersion can prepared was calculated on the basis of heat of fusion of physical mixtures of indomethacin and Crospovidone with various weight ratios.

Jinichi Fukami[48] et al., (2006) prepared rapidly disintegration tablet in the oral cavity was prepared using glycine as a disintegrants. The effect of disintegrants and the disintegration behavior of the tablet in the oral cavity were evaluated. The wetting period from carboxymethylcellulose having the hardness four kilo was three seconds .It does not affect the release of amoxicillin from the tablet.

P.S Mohanachandran[49] et al., (2011) used superdisintegrants to improve the efficacy of solid dosage forms. This is achieved by decreasing the disintegration time which in turn enhances drug dissolution rate. Disintegrants are substances or mixture of substances added the drug formulation that facilitates the breakup or disintegration of tablet or capsule content into smaller particles that dissolve more rapidly than in the absence of disintegrants. Superdisintegrants are generally used at a low level in the

solid dosage form, typically 1- 10 % by weight relative to the total weight of the dosage unit, various kinds of superdisintegrants which are being used in the formulation to provide the safer, effective drug delivery with patient's compliance.

B.Preetha[50] et al., (2004) studied croscarmellose sodium, sodium starch glycolate and crospovidone on dissolution of three model drugs with varying aqueous solubility, like carbamazepine , acetaminophen and cetrizine HCl from their respective tablet formulations prepared by wet granulation . Crospovidone in general was effective in improving the dissolution of the drugs used in the study and generally extragranular mode of addition seemed to be the best mode of incorporation, irrespective of the solubility of the main tablet component.

T.Y.Puttewar[56] et al., (2010) developed doxilamine orodispersible tablets were developed with considerable increase in drug release as compared to marketed formulations; seven formulations were developed and studied. To prevent bitter taste and unacceptable odor of the drug, the drug was taste masked with weak cation exchange resins like Indion 234, Indion 204 and Indion 414. The drug was characterized according to different compendia methods, on the basis of identification by UV spectroscopy,pH, organoleptic properties and other tests. Among the three resins, one was selected for further studies i.e., Indion 234, because of high drug loading capacity. Maximum loading was obtained at drug–resin ratio 1:2, pH 5, temperature 50°C and drug concentration 4 mg/ml. A successful taste masking of resinate was confirmed by time intensity method and also by taking drug release in 0.01 N hydrochloric acid and in simulated salivary fluid. The optimized batch with disintegration time 25.24 ±0.75 and dissolution 100.46% ± 3.78.Compared with conventional marketed formulation and was found superior.

Shaik Harun[57] et al., (2011) prepared salbutamol sulfate using super disintegrating agents. Recently fast disintegrating drug delivery system have started gaining popularity and acceptance as new drug delivery system, because they are easy to administer and lead to better patient compliance. Direct compression technique was used as it requires conventional tablet machinery and thus economical process. Formulations containing Indion as super disintegrating agent show rapid in-vitro dispersion time as compared to other formulations.

A.Abdelbary[62] et al., (2009) formulated famotidine ODT using the economic direct-compression method. A 32 full factorial design was used to evaluate the influence of different excipients on the properties and in vitro dissolution of famotidine ODT. Disintegrants were studied in three levels viz. Ac-Di-Sol, sodium starch glycolate and low-substituted hydroxy propyl cellulose maximum dissolution and minimum oral disintegration time (11.4 s) were observed in optimized prepared using L-HPC and mannitol.

Simone Schiermeeier[65] et al., (2009) formulated ibuprofen to prevent bitter taste and side effects of the drug, the drug was associated with Phospholipon 80H, a saturated lecithin, by wet granulation. The granules were then coated using different film forming agents. Coated granules were then formulated with a sweetener a mannitol-based diluent were added as superdisintegrants and compacted under low compression force. The eight lots of tablets were assessed if suitable as oral disintegrating tablets by determination of a range of technological parameters. Wetting and disintegration time matched with the requirements of for almost all these formulations. Dissolution profiles suggested that the combined action of the hydrophobic lecithin and the coating delay the release of the drug from tablets with respect to when it is free or in the form of simple granules.

C.Ferrero[66] et al., (1997) developed croscarmellose sodium (Ac-Di-Sol) in a direct compression formulation containing a poorly water soluble drug (albumin tanate) at high dosage. An experimental design with two variables, applied pressure and concentration of Ac-Di-Sol allowed the evaluation of microstructural, mechanical and disintegration properties of the tablets. Tablet properties evaluated were affected by both variables, while compression parameters were essentially dependent on applied pressure. The shortest disintegration time was found for mixtures more prone to plastic deformation and densification at same level of applied pressure. These mixtures also revealed a finer pore structure. the results, consolidation mechanism and microstructure analysis should be performed while optimizing disintegration response in tablets formulated with a disintegrants mainly acting by swelling mechanism.

Kalpesh Gaur[67] et al., (2011) prepared aceclofenac by subliming method with two super-disintegrants, crospovidone and sodium starch glycolate were used in different ratio (2-8 % w/w) with camphor as subliming agent. The prepared batches of tablets were evaluated for thickness, weigh variation, hardness, friability, drug content uniformity, wetting time, water absorption ratio, in-vitro disintegration time and in-vitro drug release. Among the three promising formulations, the formulation prepared by using 8% w/w of crospovidone and emerged as the overall best formulation based on the in-vitro drug release characteristics.

Mohanchandran P.S[68] et al., (2010) formulated amlodipine besylate using different superdisintegrants were prepared by direct compression method. FDT's were evaluated for its physicochemical properties and in vitro dissolution. Effect of different superdisintegrants on disintegration behavior of tablets was evaluated in phosphate buffer pH 7.2. All formulations were evaluated for pre□compression and post□ compression parameters. Wetting time of formulations containing croscarmellose sodium was least and tablets showed fastest disintegration. FT□IR studies revealed that there was no physico□chemical interaction between amlodipine besylate and other excipients. Optimized formulations showed short dispersion time with maximum drug release in 30 minutes. Combinations of super disintegrants were found to be better in the formulation of fast dissolving tablets of Amlodipine besylate rather than using alone.

Sandeep B[69] et al., (2009) formulated olanzapine, quick dispersing tablets by direct compression method. Effect of super disintegrant crospovidone on wetting time, disintegration time, drug content and in vitro release have been studied. A 32 factorial design was employed in formulating a quick dispersible tablet. The selected independent variables crospovidone and hydroxy propylcellulose showed significant effect on dependent variables i.e. disintegration time and percent drug dissolved. Disintegration time and percent drug dissolved decreased with increase in the level of crospovidone.

Yoshio Kuno[70] et al., (2008) prepared OD tablets were produced by directly compressing a mixture containing lactose–xylitol granules, disintegrant, glidant and lubricant, and subsequent heating. The effect of the type of lubricant on the tablet

characteristics was evaluated using magnesium stearate (Mg-St), sodium stearyl fumarate (SSF), and talc as lubricants. The hardness of the tablets increased to as a result of heating, regardless of the kind of lubricant. The oral disintegration time of the tablets containing increased with an increase in the hardness. The oral disintegration time of the tablets containing talc was not changed despite of an increase in hardness.

Grega Klancnik[71] et al., (2010) comprised a group of techniques in which a physical property of a substance is measured to a controlled temperature program. The results given from the DTA or DSC curves depend on the preparation of the material, and on the instrument sensitivity. The sensitivity is in close relation to the apparatuses design. Several types of DTA and DSC apparatuses are described as well as the use. New types of DSC devices are being developed which will have the capability of high heating / cooling rates and with shorter response time.

Rahul Chandrasekhar[73] et al., (2009) studied series of hardness, fracturability and disintegration time tests were performed on the formulations at each stage. During Stage I, tablets were prepared in concentrations between 2% and 5% w/w, and were formulated at each concentration as single and combination bloom strength gelatin using 75 and 225 BSGs. Analysis revealed that both hardness and disintegration time increased with an increase in gelatin concentration. A combination FDT comprising a 50:50 ratio of 75:225 BSGs (hardness: 13.7 ± 0.9 N and disintegration time: 24.1 ± 0.6 s) was judged the most ideal, and was carried forward to Stage II: the addition of the saccharides sorbitol, mannitol and sucrose in concentrations between 10% and 80% w/w.

J.M Gines[74] et al., (1995) studied the analytical thermal techniques employed , differential scaning calometry(DSC) and hot stage microscopic, has demonstrated the ability of melted gelucire 53/10 to dissolve the crystals of cinnarazine. The high solubilizing effect of these vehicles, in comparison with other carriers, may be explained on the basis of its surfactants properties. Only at low drug percentages, can total dissolution of the cinnarazine present in the system be achieved.

Faizi Muzaffar[75] et al., (2010) formulated amoxicillin microsphere were formulated by using solvent evaporation technique using Eudragit RS 100 matrix polymer. Evaluation of the prepared microsphere were done for the percentage yield, particle size analysis, particle size distribution, angle of repose, and determination of the drug content, shape, surface characterization, drug entrapment.

A.K.Hilton[76] et al., (1992) investigated hydrophilic polymers were investigated for the preparation of amoxicillin trihydrate SR tablets. The most suitable system contain a 1:2 ratio of HPC to drug, which compressed easily and was not affected by alteration in normal compaction pressure. The dissolution showed that linear release of drug from matrix. Formulation of enhanced gastric retention time, by incorporation of gas-generating system, yielded either bilayer tablets which prematurely failed or large single layer tablet which remain buoyant for 6hours and showed satisfactory in vitro sustained release.

N.Visavarungroj[77] et al., (1990) studied cross-linked starches and pregelatinized-crosslinked starches were evaluated as disintegrating agents in comparison to potato starch and a number of super-disintegrants such as Ac-Di-Soi, Explotab and Polyplasdone XL. The influence of disintegrants concentration, tablet hardness and tablet additives was evaluated by measuring the disintegration time of the tablets. Potato starch and the starches that were crosslinked only showed the lowest granule swelling power. The considerable swelling power achieved for the pregelatinized or pregelat starches, both the rate and amount of water uptake were observed to be low for these forms.

Kimberley Jackson[78] et al., (2000) studied physicochemical and physiological processes that can be altered by drug–excipient interactions and to explore mechanisms by which they might occur.

Lucy S.C[79] et al., (1989) observed glycolate to have a higher DT and lower water uptake at higher concentrations of the disintegrants. With, the DT increased with increasing viscosity of MC. This occurs despite an increase in water uptake by tablets containing higher viscosity MC. For tablets containing SiO, and MC, DT is extremely high. In the absence of MC, water uptake is slightly higher with the higher

concentration of SiO, but DT still remained high. Water uptake alone does not determine the disintegration process. The choice of excipients, especially binders such as methylcellulose, plays a crucial role in influencing disintegrants action.

G.K.Bolhuis[80] et al., (1997) studied as an effect of its lower swelling power, the super disintegrant crospovidone is far less effective than the other super disintegrants. Wet granulation of poorly soluble drugs with high concentrations of sodium starch glycolate resulted likewise in a strongly improved drug release and bioavailability from capsules and tablets. It was found, however, that granules containing a too high concentration of the super disintegrant slow down the drug release from tablets. This effect is caused by the formation of a viscous barrier of the super disintegrant in the granules during the dissolution process.

Gopa Roy Biswas[82] et al., (2011) prepared amoxicillin trihydrate by solid dispersion technique using modified gum karaya as a carrier. FTIR spectroscopy was performed to study drug polymer interactions. No drug polymer interaction was found. As confirmed by FTIR studies. The drug was dissolved in ethanol with continues stirring up to 30 min. Polymer was suspended in sufficient amount of water the drug solution was poured in to polymer suspension. The entire solvent was evaporated to 60°C-70°C. Four formulation were prepared at adrug polymer ratio of 1:1,1:2,1:3,1:4. The result of solubility study showed with the increase in concentration of polymer. The modified gum karaya can be well utilized to increase to solubility of poorly water soluble drug amoxicillin trihydrate.

3.1. AIM AND OBJECTIVE

The dispersible tablet is one of the most successful and famous dosage forms in the pharmaceutical market. Many of the dosage form that have been developed had not reached the market due to the high cost of manufacturing or due to the patient inconvenience but dispersible tablet have been dominating the market since the development of the dosage form. Dispersible tablet dosage form which is mostly prescribed in elderly, pediatric and aphagia patients. So the dispersible tablet is one of the most preferred dosage forms in the pharmaceutical market, WHO prefer dispersible tablet for elderly and paediatric patients. The market value of the dispersible tablet in developed countries is very high comparing to the developing countries. Most of the Indian pharmaceutical industries manufacture large value of dispersible tablet for the export.

Amoxicillin is a semisynthetic aminopencillin with a broad-spectrum bactericidal activity used as trihydrate in oral preparation. Amoxicillin trihydrate have been widely used β lactum antibiotic in most of the African and European countries. Most of the antibiotic which are prescribed in the dispersible tablet dosage forms, due to the high manufacturing cost they are mostly manufactured developing countries like India, Brazil and china etc. it is one of the most profitable export business in the pharmaceutical industry and most of the industries in India have participated in this by making it a value of 547 crores at the year 2009-2010. By the proper management of the raw material and the method the export of the amoxicillin trihydrate can be more profitable and they can provide the patient in an affordable manner.

In this work the challenge is to develop a formulation of amoxicillin trihydrate dispersible tablet of 320 mg in a low production value by using any method. Currently the industry is producing amoxicillin trihydrate dispersible tablet at much higher production rate, due to the high value of the raw material used in the industry. In this work tablets were developed using amoxicillin trihydrate which is purchased from a different supplier of lower price than the amoxicillin trihydrate currently using now, by the development of the tablet with this material, will results in tablets with low production rate. Earlier works done with the new material had resulted in the poor dissolution and disintegration of the tablet. So the entire preformulation and the

evaluation of the tablet have to be done to develop an economical amoxicillin trihydrate DT, which shows good dissolution properties and disintegration time.

- Formulation and evaluation of dispersible tablets of β lactum antibiotic drug.
- Improvement of the drug dissolution profile by disintegrants in the formulation.
- To study the effect of disintegrants concentration on the dissolution profiles of drug containing formulations.
- To determine the chemical compatibility of formulation containing various ratio of polymer and drug.
- To study the stability of the drug in different environmental condition.
- To determine the thermal stability of the drug and the tablet.

3.2. PLAN OF WORK

The study was planned to carry out as follows

1. Procurement of drug, polymer and other excipients
2. Preparation of mixed blend of drug and excipients by using super disintegrants
3. Checking Drug and excipients compatibility by FTIR studies
4. Evaluation of powder mixed blend of drug and excipients
5. Compression of tablet by “Direct Compression method”
6. Evaluation of compressed tablets
7. In-vitro drug release
8. DSC studies
9. X-ray diffraction studies
10. Stability testing of optimized batch
11. Kinetics of drug release

5. Materials and Equipment used

- **List of Chemicals**

Table No.2

Sl.No	Materials Used	Supplied by
1	Amoxicillin trihydrate (Work)	Zhuhai, China
2	Dispersible cellulose	Micro Labs, Banglore
3	Starch	Micro Labs, Banglore
4	Maize starch	Micro Labs, Banglore
5	Crospovidone	Micro Labs, Banglore
6	Sodium starch glycolate	Micro Labs, Banglore
7	Croscarmellose	Micro Labs, Banglore
8	Magnesium Stearate	Micro Labs, Banglore
9	Colloidal Silicon	Micro Labs, Banglore

- **List of Equipments**

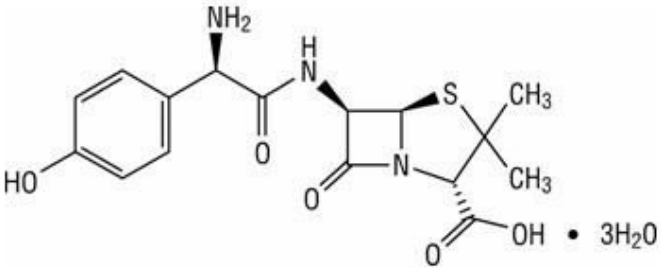
Tablet No.3

Sl No	Equipments	Supplied by
1	Single pan digital balance	Mettler Toledo, Switzerland.
2	Octagonal blender	India octagonal blender, India.
3	Tap Density Tester	Electro Lab, India.
4	Vernier Calipers	Mitutoyo, USA.
5	UV-Visible spectrophotometer	UV 1700 shimadzu, Japan.
6	Dissolution apparatus	Lab India, India.
7	Double rotary punching machine	Cad Mach, India.
8	Hardness tester	Dr. Schleuniger, Switerland.
9	Tablet Friabilator tester	Electro Lab, India.
10	Disintegration tester	Electro Lab, India.
11	Stability Chamber	Newtronics, India.
12	HPLC	LC-2010 AHT, Japan.
13	Moisture content analyser	Medttler Toleo, Switerland.

5.1. DRUG PROFILE

AMOXICILLIN TRIHYDRATE[16,17,19,20,21,23,26]

Structure:



Chemistry

Molecular formula: $C_{16}H_{19}N_3O_5S \cdot 3(H_2O)$

IUPAC Name: (2S,5R,6R)-6-[[(2R)-2-Amino-2-(4-hydroxyphenyl)acetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid trihydrate.

Molecular Weight: 419.45

Melting Point: 194ºC

$_P$Ka : 9.48

Solubility:

Slightly soluble in water, very slightly soluble in ethanol (96 per cent), practically insoluble in fatty oils. It dissolves in dilute acids and dilute solutions of alkali hydroxides.

Appearance:

White or almost white, crystalline powder.

Category:

β lactum antibiotics

Pharmacology:

Used to treat bacterial infections caused by susceptible microorganisms

Mechanism of action[17]:

Amoxicillin trihydrate interfere with the synthesis of bacterial cell wall. The bacteria synthesize UDP-N-acetylmuramic acid pentapeptide and UDP-N-acetyl glucosamine. The peptidoglycan residues are linked together forming a long strands and UDP spilt off. The final stage is cleavage of the terminal D-alanine of the peptide chains by transpeptidase; the energy so released is utilized for the establishment of cross linkages between peptide chains of the neighbouring strands. This cross linking provides stability and rigidity to the cell wall. The amoxicillin inhibit the transpeptidase so that the cross linking does not occur.

Side effects[26]:

Local irritancy and direct toxicity, hypersensitivity, candida stomatitis or vaginitis and rashes with intense itching, some cases of hepatic toxicity have been reported.

Pharmacokinetics

Absorption:

Amoxicillin oral absorption is rapid and complete. Amoxicillin is rapidly absorbed by the gastrointestinal tract after oral administration and is stable in the presence of gastric acid. Food does not interfere with absorption. Peak serum concentrations are usually attained within 1 to 2 hours following oral administration. After the oral administration of 500mg amoxicillin trihydrate the Cmax is 6.0-15.3, tmax is 2 hour. The AUC(Area under the curve) ranged from 21.0 to 30.3 mg/liter/hour with a mean of 27.4mg/liter per hour.

Distribution:

Amoxicillin diffuses readily into most body tissue and fluids, with the exception of the cerebrospinal fluid; Pleural fluids, lungs, and peritoneal fluid; high urine concentrations are attained; also into synovial fluid, liver, prostate, muscle, and gallbladder; penetrates into middle ear effusions, maxillary sinus secretions, tonsils, sputum, and bronchial secretions, although higher concentrations of the drug may be attained in patients with inflamed meninges. Amoxicillin is not highly protein bound

about 17% - 20%. Its elimination half-life ranges from 0.7 to 1.4 hours in patients with normal renal function. Amoxicillin is partially metabolized to microbiologically inactive metabolites.

Excretion:

Amoxicillin is excreted through urine (60% unchanged). Small amounts of the compounds are excreted in feces and bile.Half-life elimination of neonates is 3-7 hours, infants and children 1-2 hours, adults with normal renal function 0.7-1.4 hours and renal impairment patient (Clcr <10 mL/minute) is 7-21 hours. In healthy adult after the administration of 500mg amoxicillin by oral/ iv administration the mean amount of amoxicillin recovered unchanged in the urine over 24 h was 287.0 mg(57.4%) after i.v. dosage and 217.1 mg (43.4%)after oral dosage.

Drug interactions:

Regular use of probenecid or other renal acid secretory system inhibitors decrease renal secretion of amoxicillin and increase blood concentration of amoxicillin. Allopurinol administered with amoxicillin may increase the possibility of skin rash. Administration of amoxicillin with other bacteriostatic drugs may interfere with the bactericidal effect. Amoxicillin will decrease the effect of oral contraceptives. It is due to the inactivation of colonic flora which may interfere with deconjugation and enterohepatic cycling of oral contraceptives causes the failure of oral contraceptives some clinicians advise alternate dosage regimen for both drugs.

It has contraindication in pregnancy state as it readily cross placenta. Its safety in treatment of infections during pregnancy has not yet established. Adverse effect has not yet been established. Amoxicillin appears in milk in low concentrations. The frequent administration of amoxicillin will result in diarrhea. It causes high incidence of rashes in patients with AIDS and lymphatic leukemia. Sometimes the rashes may be toxic in nature. It also produces local irritancy and direct toxicity, hypersensitivity like urticarial, angioedema, bronchospasm and jarisch –Herxheimer reaction.

Contraindication:

Amoxicillin trihydrate is contra indicated in patients with:

- Allergic to penicillin and other beta-lactam antibiotics
- Allergic to any of the active ingredients in the medicine
- Glandular fever
- Asthma patient
- Pregnant Patients
- Breast feeding
- Acute or chronic impairment

Side effects:

Patients administering amoxicillin trihydrate may suffer from mild side effects. These side effects may include:

- Headaches
- Gastrointestinal distress
- Vomiting
- Stomach aches
- Swollen tongue
- Development of white patches on the tongue and sides of the mouth.
- Seizures
- Nausea
- Rashes with severe itching
- Flu-like symptoms such as a fever and sore throat, along with changes to a
- Mental or emotional disturbances

Therapeutic use

- Upper respiratory tract infection.
- Genitourinary tract infection.
- Skin and soft tissue infection.
- Lower respiratory infection
- Syphilis
- Gonorrhoea
- Diphtheria
- Tetanus
- Chronic urinary tract infections
- H.pyloric infection

Dosage

Adults:

- Adult dose 250 mg every eight hours.
- In Gonorrhoea 3 gm of amoxicillin with one gram of probenecid should be given as a single dose.
- In severe infections or those caused by less susceptible organisms 500 mg every 8 hours for adults.

Children:

- 20 mg/kg/day in divided doses every 8 hours.
- In gonorrhea, 50 mg/kg body weight and 25 mg of probenecid per kg of body weight should be given as a single dose. Probenecid is not recommended in children under 2 years of age.

5.2. POLYMER PROFILE[4,18,25]

CROSSCARMELLOSE SODIUM

Nonproprietary Names:

BP: Croscarmellose sodium

PhEur: Carmellosum natricum conexum

USPNF: Croscarmellose sodium

Synonyms:

Ac-Di-Sol; cross linked carboxymethylcellulose sodium; *Explocel*; modified cellulose gum; Nymcel ZSX; *Pharmacel XL;* Primellose; *Solutab;* Vivasol.

Functional Category:

Tablet and capsule disintegrants.

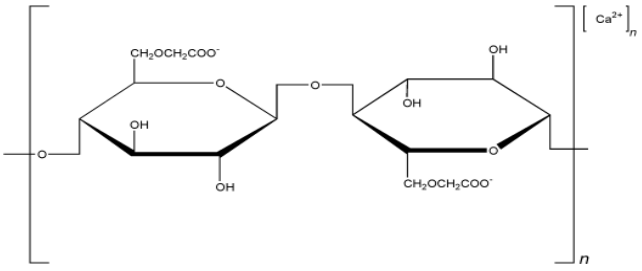
Chemical name:

Cellulose carboxymethyl ether calcium salt.

Empirical Formula and Molecular Weight:

The USPNF 23 describes carboxymethylcellulose calcium as the calcium salt of polycarboxymethyl ether of cellulose

Structural Formula:



Applications in Pharmaceutical Formulation or Technology:

- Used as a disintegrant for capsules, tablets, and granules**.**
- Croscarmellose sodium may be used in both direct-compression and wet-granulation processes in tablet formulations.
- Wicking and swelling ability of the disintegrant is best utilized when used in wet granulations.
- Used both the wet and dry stages of the process (intra and extra granularly).
- Croscarmellose sodium at concentrations up to 5% w/w may be used as a tablet disintegrant, 2% w/w is used in tablets prepared by direct compression and 3% w/w in tablets prepared by a wet-granulation process.

Uses of Croscarmellose Sodium:

Use	**Concentration (%)**
Disintegrant in capsule	10-25
Disintegrant in tablets	0.5-5.0

Description:

Croscarmellose sodium occurs as an odorless, white or greyish-white powder.

Incompatibilities:

The efficacy of disintegrants, such as Croscarmellose sodium, may be slightly reduced in tablet formulations prepared by either the wet-granulation or direct-compression process that contain hygroscopic excipients such as sorbitol.

Croscarmellose sodium is not compatible with strong acids or with soluble salts of iron and some other metals such as aluminum, mercury and zinc.

Stability and Storage Conditions:

Croscarmellose sodium is a stable though hygroscopic material. Croscarmellose sodium should be stored in a well-closed container in a cool, dry place.

SODIUM STARCH GLYCOLATE

Nonproprietary Names:

BP: Sodium starch glycolate

PhEur: Carboxymethylamylum natricum

USPNF: Sodium starch glycolate

Synonyms:

Carboxymethyl starch, sodium salt; *Explosol*; *Explotab*; *Glycolys*; *Primojel*; starch carboxymethyl ether, sodium salt; *Tablo*; *Vivastar P*.

Chemical Name:

Sodium carboxymethyl starch.

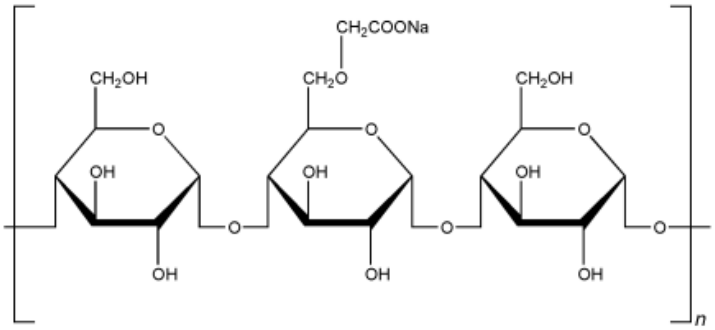
Empirical Formula and Molecular Weight:

The USPNF 23 states that sodium starch glycolate is the sodium salt of a carboxymethyl ether of starch.

The PhEur 2005 describes three types of material: Types A and B occurs as the sodium salt of a cross-linked partly *O*-carboxymethylated potato starch, containing 2.8–4.2% and 2.0–3.4% of sodium respectively. Type C is the sodium salt of a cross-linked by physical dehydration, partly *O*-carboxymethylated starch containing 2.8–5.0% sodium.

Sodium starch glycolate may be characterized by the degree of substitution and crosslinking. The molecular weight is typically 5×10^5–1×10^6.

Structural Formula:



Functional Category:

Tablet and capsule disintegrant.

Applications in Pharmaceutical Formulation or Technology:

- Sodium starch glycolate is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations.
- It is commonly used in tablets prepared by either direct-compression or wet- granulation processes.
- The concentration employed in a formulation is between 2% and 8%, with the optimum concentration about 4%.
- Disintegration occurs by rapid uptake of water followed by rapid and enormous swelling.
- By use of sodium starch glycolate, increasing the tablet compression pressure also appears to have no effect on disintegration time.
- Sodium starch glycolate has also been investigated for use as a suspending vehicle.

Description:

Sodium starch glycolate is a white to off-white, odorless, tasteless, free-flowing powder. It consists of oval or spherical granules, 30–100 μm in diameter, with some less-spherical granules ranging from 10–35 μm in diameter.

Incompatibilities:

Sodium starch glycolate is incompatible with ascorbic acid.

Stability and Storage Conditions:

Tablets prepared with sodium starch glycolate have good storage properties.Sodium starch glycolate is stable and should be stored in a well-closed container in order to protect it from wide variations of humidity and temperature, which may cause caking.

The physical properties of sodium starch glycolate remain unchanged for up to 3–5 years if it is stored at moderate temperatures and humidity.

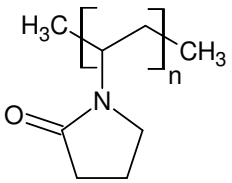
CROSPOVIDONE

Crospovidone is a cross-linked homopolymer of 1-ethenylpyrrolidin-2-one. It is available in different degrees of powder fineness (type A and type B).

Molecular Formula: $(C_6H_9NO)_n$-$(C_4H_6O_2)_m$

Molecular Weight: 5000-70000

Structural Formula:



Description: White or yellowish-white powder or flakes, hygroscopic.

Density, tapped: 0.35-0.45 gm/cm^3

Solubility: Practically insoluble in water, in alcohol and in methylene chloride.

Stability & storage conditions: Crospovidone is a stable and should be stored in a well-closed container in a cool and dry place.

Incompatibilities:

Crospovidone is incompatible with most inorganic and organic pharmaceutical ingredients. When exposed to high water levels, Crospovidone may form molecular adducts with some materials.

Handling procedures:

Eye protectors, gloves and dust mask are recommended.

Uses:

Crospovidone is used in oral pharmaceutical formulations and as a disintegrants for capsules, tablets and granules.

DISPERSIBLE CELLULOSE

Dispersible Cellulose is a colloid-forming, attrited mixture of Microcrystalline Cellulose and Carmellose Sodium.

Synonym: Avicel RC

Chemical Name:

A cellulose having some of the hydroxyl groups in the form of the methyl ether

Category:

Pharmaceutical aid (lubrication, tablet and capsule adjuvants)

Description:

A white or off-white, coarse or fine powder.

Solubility:

Soluble in water and when disperses in *water* producing a white, opaque dispersion or gel; practically insoluble in organic solvents and in dilute acids.

Application and uses:

Dispersible celluloses are used in pharmaceutical suspensions, emulsions, nasal sprays, and creams. The wide range of thixotropies, viscosities, gel strengths, and dispersion characteristics of this product line provide unparalleled suspension stability and functional versatility.

Stability and Storage:

Dispersible Cellulose should be stored at a temperature of 8°C to 15°C.

MAIZE STARCH

Maize starch is obtained from caryopsis of *Zea mays L.*

Nonproprietary Name:

B.P: Maize starch

U S P: Starch

Ph Eur: Corn starch

Functional Category:

Pharmaceutical Excipient

Molecular Formula:

$(C_6H_{10}O_5)n$

Application in pharmaceutical Formulations:

- Binding agent
- Disintegrating agent
- It is widely used as a filler or diluent in tabelts and in capsules.

Description:

White to yellowish in colour, very fine powder with creaks when pressed between fingers.

Solubility:

Practically insoluble in cold water and ethanol (96%).

Storage: Store in a cool dry place, avoid moisture.

5.3. EXCIPIENTS PROFILE[4,18,15]

MAGNESIUM STEARATE

Nonproprietary Names

BP: Magnesium stearate

JP: Magnesium stearate

PhEur: Magnesii stearas

USPNF: Magnesium stearate

Synonym

Magnesium octadeconate, Octadecanoic acid, Magnesium salt, Stearic acid, magnesium salt.

Chemical name

Octadeconic acid magnesium salt.

Empirical formula

$C_{36}H_{70}MgO_4$.

Molecular weight

591.34

Composition

The USPNF 23 describes magnesium stearate as a compound of magnesium with a mixture of solid organic acids that consists chiefly of variable proportions of magnesium stearate and magnesium palmitate ($C_{36}H_{70}MgO_4$). The Ph. Eur 2005 describes magnesium stearate as a mixture of magnesium salts of different fatty acids consisting mainly of stearic acid and in major proportions other fatty acids.

Structural Formula

$[CH_3 (CH_2)_{16}COO]_2Mg$

Functional category

Tablet and capsule lubricant

Pharmaceutical Applications

- Magnesium stearate is widely used in cosmetics, foods and pharmaceutical formulations.
- It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0%.
- It is also used in barrier creams.

Description

Magnesium stearate is a very fine, white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to touch and readily adheres to the skin.

Incompatibilities

Incompatible with strong acids, alkalis and iron salts. Avoid mixing with strong oxidizing materials. Magnesium stearate cannot be used in products containing aspirin, some vitamins and most alkaloidal salts.

Safety

Magnesium is generally regarded non-toxic following oral administration. However overconsumption of large quantities may cause laxative effect and mucosal irritation. No toxicity information is available relating to normal routes of occupational exposure.

Stability/storage conditions

Magnesium stearate is stable and should be stored in a well closed container in a cool dry place.

COLLOIDAL SILICON

Nonproprietary Names

BP: Colloidal anhydrous silica

PhEur: Silica colloidalis anhydrica

USPNF: Colloidal silicon dioxide

Synonym

Aerosil ;Cab-O-S*il*;Cab-O-S*il* *M* -5P;colloidal silica;fumed silica;light anhydrous silicic acid;silicic anhydride; silicon dioxide fumed;

Chemical name

Silica {7631-86-91}

Empirical formula

SiO_2

Molecular weight

60.08

Composition

Despite the fact that colloidal silica has the same chemical formula as quartz sand, SiO2, the two materials could hardly be more different in their effect on paper machine operations. The key difference is size. The subunits of colloidal silica particles are typically in the range of 1 to 5 nm. Whether or not these subunits are joined together depends on the conditions of polymerization. Initial acidification of a water-glass (sodium silicate) solution yields Si(OH)4. If the pH is reduced below 7 or if salt is added, then the units tend to fuse together in chains.

Structural Formula

Sio_2

Functional category

Adsorbent, anticaking agent, tablet disintegrants, viscosity increasing agent.

Pharmaceutical Applications

- Used in aerosols.
- Emulsion stabilizer.
- Glidants.
- Suspending agent and thickening agent.
- Tablet disintegrants.

Description

Colloidal silicon is a submicroscopic fumed silica with a particle size of about 15 nm. It is a light, loose, bluish-white coloured, odourless, tasteless, gritty, fluffy powder.

Incompatibilities

Incompatible in diethyl stillbestrol preparations

Safety

Intraperitoneal and subcutaneous injection may produce local tissue reactions and/or granulomas.

Stability/storage conditions

Colloidal silicon dioxide is hygroscopic but adsorbs large amount of water without liquefying. When used in aqueous systems at a pH 0±7.5, colloidal silicon dioxide is effective in increasing the viscosity of a system.

6. EXPERIMENTAL WORKS

Preformulation studies

Identification tests:[13,44]

UV spectra:

Amoxicillin trihydrate is dissolved in a suitable solvent and it was scanned at wavelength 200nm-400nm in which 0.1N HCL as a blank, using double beam UV/Visible spectrophotometer. The maximum wavelength was found to be 272nm.

IR spectra:

The IR spectra of drug in KBR pellets at moderate scanning between 4000-400 cm^{-1} was carried out using FTIR (Perkin Elmer). The spectrum gives the peak value of the compound, when comparing with the standard value of the functional group. The sample was identified as pure amoxicillin trihydrate drug.

Solubility:

It is slightly soluble in water, ethanol (95%), and methanol. It is insoluble in chloroform, ether and in fixed oils. It is soluble in dilute solutions of acids and alkali hydroxides.

Drug excipient compatibility studies:[17]

Drug-Excipient compatibility studies form an important part of Preformulation studies. The interaction between the drug and excipients are determined after a specific time period by using suitable analytical technique like FTIR.

Preparation of stock solution:[33,34,40]

Amoxicillin trihydrate was accurately weighed and transferred in to the 100 ml volumetric flask. It was dissolved in 0.1 N HCL and the volume were made up to the mark with 0.1 N HCL to get a 1000 µg/ml solution. 2 ml of the above solution was then further transferred in to another 100 ml standard flask and made up to 100 ml with 0.1 N HCL to get stock solution of 20 µg/ml.

Preparation of Standard curve:

From the stock solution 1 - 10 ml were pipetted out in to 10 ml volumetric flask and were made up to the mark with 0.1 N HCL to obtain amoxicillin trihydrate concentration of 2 - 20 µg/ml respectively. Absorbance of each solution was measured at 272nm.

Sl No.	Concentration (mcg)	Absorbance
1	2	0.077
2	4	0.144
3	6	0.224
4	8	0.291
5	10	0.362
6	12	0.440
7	14	0.510
8	16	0.581
9	18	0.653
10	20	0.725

Calibration Curve

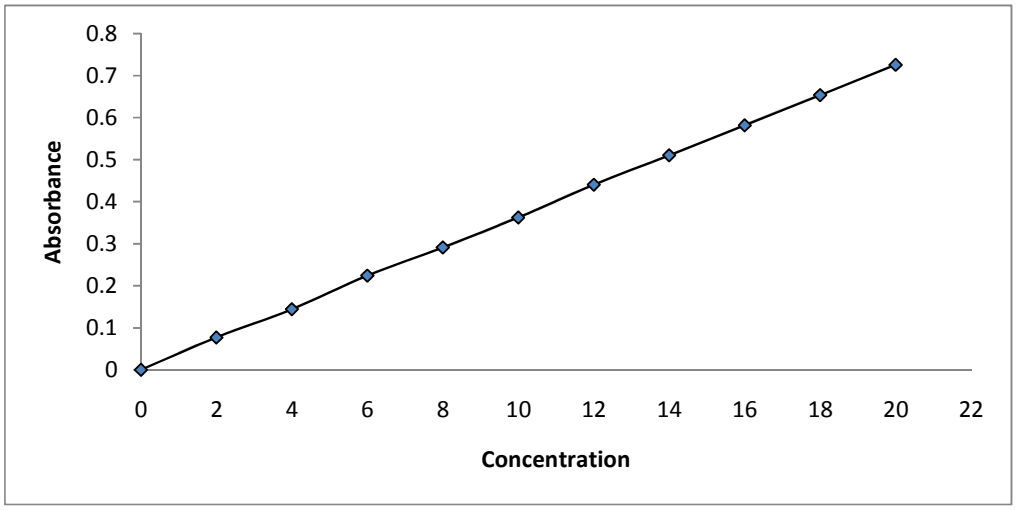


Figure 1

Regression= 0.9999

Preformulation studies of pure drug and excipients:[3,5,29,30,57,32]

It is the first step in the rational development of dosage forms of a drug substance, these studies focus on those physicochemical properties of the drug that could affect drug performance as an effective drug dosage form. Preformulation can also be defined as the investigation of physical and chemical properties of a drug substance alone or with excipients. It will provide the necessary information for the development of safe, stable and effective formulation. Following Preformulation studies are done with the sample drug.[3]

Objective*:*

The overall objective of preformulation testing is to generate information useful to the formulation in developing stable and bioavailable dosage forms.

Scope: The use of preformulation parameters maximizes the chances in formulating an acceptable, safe, efficacious and stable product.

Bulk Density (D_b):

Bulk density of a compound varies substantially with the method of crystallization, milling or formulation. It is of great importance when one considers the size of a high dose capsule product or the homogencity of a low dose formulation in which there are large differences in drug and excipient densities. In addition to bulk density, it is frequently desirable to know the true density of a powder for computation of void volume or porosity of packed powder beds.

Apparent bulk density is determined by taking weighed quantity of the powder (W) in a graduated measuring cylinder and volume (V_0) was measured, then bulk density was calculated by using the formula,

Bulk density = weight of powder/ volume of powder
B.D. = W/V_0 g/ml

Tapped Density (D_i):

Weighed amount of powder was taken in a graduated cylinder and the volume was measured (Vo). The graduated cylinder was fixed in the tapped densitometer and tapped on a hard surface from the height of 10 cm at 2 second interval until the difference in the volume after consecutive tapping was not changed. The final reading was denoted by (V_f) the volume of blend was used to calculate the tapped density, hausner's ratio and Carr's index.

Tapped density =W/V_f g/ml

Where W = Weight of the powder

V_0 = Initial volume

V_f = final volume

Angle of repose (θ):

The angle of repose is the measurement of the friction between the particles. Powder consists of individual particles of different size and shape. It is consider in the flow of the powder during the mixing of powders, flow of the powder in hopper, flow between die cavity and punches. It is the angle between free standing surface of powder and horizontal plane. Low value of angle of repose means flow of the particles or the friction between them is high. In these cases the friction between the particles can be increased by the use of friction reducing agent or "Glidants" eg: lactose.

The Angle of Repose can be calculated using the formula :

$\tan\theta = h/r$

h= height of the pile (cm)

r= radius of the pile (cm)

The powder was allowed to flow through a funnel fixed on a stand at a definite height (h) and powder will fall on the surface below the funnel forming a pile, radius of the pile is noted (r). Care was taken to see that the particle doesn't fall or slip during the whole procedure.

Relationship between angle of repose and flow property is

Standard angle of repose as per flow properties

Table No.4

Sl no	Angle of repose	Type of flow
1	<20	Excellent
2	20-30	Good
3	30-40	Passable
4	>40	Very Poor

Carr's Compressibility Index:[5,32]

An indirect method of measuring powder flow from bulk densities was developed by Carr. The percentage compressibility of a powder was a direct measure of the potential powder arch or bridge strength and stability. Carr's index of each formulation was calculated according to equation given below:

Carr's Compressibility Index (%) = [(TD-BD) X 100] / TD

Where, TD = Tapped density and BD = bulk density

Relationships between % Compressibility and Flowability:

Table No.5

Sl. No.	% Compressibility	Flowability
1	5 – 15	Excellent
2	12 – 16	Good
3	18 – 21	Fair to Passable
4	23 – 35	Poor
5	33 – 38	Very Poor
6	> 40	Extremely Poor

Hausner's Ratio:[5]

Hausner's Ratio indicates the flow properties of the powder and is measured by the ratio of tapped density to bulk density. It is the ratio of tapped density and bulk density. Hausner found that this ratio was related to inter particle friction and, as such, could be used to predict powder flow properties. Generally a value less than 1.25 indicates good flow properties, which is equivalent to 20% of Carr's index.

Hausner's Ratio = Tapped density/Bulk Density

Significance of Hausner's ratio

Table No.6

Sl. No.	**Hausner's Ratio**	**Property**
1	0–1.2	Free flowing
2	1.2–1.6	Cohesive powder

PREPARATION OF TABLETS:[31-33,58-67]

Selection of tablet punching method

While selecting the tablet punching method, compressibility character of the active substance and the excipients should be considered. For drugs, which are poorly compressible and have moderate to high dose, the wet granulation method would be followed.

Drugs with low to moderate doses and good flow property direct compression method will be more advantages in term of economy, stability and performance.

In this formulation amoxicillin trihydrate dispersible tablet are prepared mainly by wet granulation and direct compression.

Selection of Excipients

Excipients are as important as the active drug in a formulation. It will play an important role in the quality and action of the formulation.

The following are used as excipients in the formulation of amoxicillin trihydrate dispersible tablet.

Disintegrants[77,78]

Less disintegration time and good dispersibility are the main characteristics of a good dispersible tablet. The necessity of the dispersible tablet is fast dispersion in a glass of water with less time. Some pharmaceutical ingredients require a binder for tableting. This provides the cohesiveness necessary for bonding together granules under compression. In such cases disintegrants are added to liberate the granules from this force and release the drug in to the solution. This demand results in the use of special disintegrants called "SUPER DISINTEGRANTS".

Disintegrants used in this formulation are maize starch, Sodium starch glycolate, Croscarmellose, Crospovidone and dispersible cellulose.

Lubricants/Glidants

Lubricant may be defined as a suitable material, a small amount of which interposed between two rubbing surface will reduce the friction arising at the interface. Mainly lubricants are intended to reduce the friction between the particles during the flow through the hopper and ejection of the tablet from the dies. In this formulation colloidal silicon and magnesium stearate are mainly used.

Particle size

The particle size range for direct compression tablets tends to be with in the 100-200 µm range, mostly because of their required compaction behavior and powder flow properties. Smaller particles have higher absorption also the particle size have important effect in almost every step including mixing, granulation, compression etc.

The size of the particle is maintained by sieving process in which a particular size range of particle will be collected which will produce an appropriate characteristic of the tablet.

Batch Calculation of Amoxicillin trihydrate dispersible tablet:

$$\text{Batch weight} = \frac{\text{Tablet weight} \times \text{Batch size} \times \text{Convertion factor}}{1000 \times 1000}$$

$$\text{Convertion factor} = \frac{\text{Molecular weight of Amoxicillin trihydrate}}{\text{Molecular weight of Amoxicillin}}$$

PREAPARATION OF AMOXICLLIN TRIHYDRATE DISPERSIBLE TABLETS

Preparation of amoxicillin trihydrate dispersible tablets by Wet granulation method[32,60-63,80]

The amoxicillin trihydrate and other excipients were weighed as per the Table no. 7. Drug and the excipients were dry mixed for 15 mins using a planetary mixer. The mixture was transferred in to a RMG(Rapid mixing granulator), to the mixture in the RMG granulating medium (purified water) was added slowly for a period of 30-180 sec at agitator on slow speed and chopper off till obtain an appropriate consistency, add additional purified water if required to get the desired consistency. Each experiment was stopped immediately at the end of the liquid addition phase, hence wet massing was not performed, operate RMG for 30-180 sec at agitator and chopper fast speed for additional time to complete the granulation. During the process the mixer impeller and chopper were set at 300 rpm and 1300 rpm respectively. The total amount of the water added was adjusted according to the granule formation.

Granules were dried by using a tray drier. Granules were spread uniformly on the tray and kept inside the tray drier, the temperature and time were set. The drying process is continued untill the moisture of the granules reaches a moisture content of 12.4% to 13.4%.

Dried granules were passed through the 22# (ASTM) sieve mesh. Finally magnesium stearate was added to the blend by passing through 22# (ASTM) sieve mesh. This blend is then mixed well and compressed in to tablet using rotary tablet machine.

Preparation of amoxicillin trihydrate dispersible tablet by Direct compression[33,62,63,81]

The amoxicillin trihydrate and other excipients were weighed accurately as per the Table no. 7, and then all the powders were passed through the 22# (ASTM) sieve mesh, except magnesium stearate which was passed through 22# (ASTM) sieve mesh. The whole blends were mixed in an octagonal blender for 5 min. Then the resulting blend was compressed in to tablets using a rotary tablet machine

Tablet Size and Shape description.

Shape and size description:

Circular flat beveled edged tablet, with upper bisects and lower plain surface. B tooling tablets.

PREPARATION OF AMOXICILLIN TRIHYDRATE DISPERSIBLE TABLETS

Table No.7

Formulation	Amoxicillin trihydrate (mg)	Dispersible Cellulose (mg)	Maize starch (mg)	Crospovidone (mg)	SSG (mg)	Croscarmellose (mg)	Mg Stearate (mg)	Colloidal Silicon (mg)	Total (mg)
F1	287	-	-	28	-	-	4	1	320
F2	287	-	-	-	28	-	4	1	320
F3	287	-	-	-	-	28	4	1	320
F4	287	28	-	-	-	-	4	1	320
F5	287	-	12.95	15.05	-	-	4	1	320
F6	287	-	12.95	-	15.05	-	4	1	320
F7	287	-	12.95	-	-	15.05	4	1	320
F8	287	-	9.33	9.33	9.33	-	4	1	320
F9	287	-	-	-	14	14	4	1	320
F10	287	-	-	14	-	14	4	1	320

287 mg of amoxicillin trihydrate = 250 mg amoxicillin

EVALUATION OF TABLETS[42,64-70]

Hardness test:

Tablet requires a certain amount of strength or hardness and resistance to withstand mechanical shock of handling in manufacture, packing and shipping. Hardness tester measured the hardness of tablet. Five tablets from each batch were used for hardness studies and results were expressed in Newton.

Thickness and diameter:

The thickness and diameter of tablets was carried out using Vernier caliper. Five tablets were used for this test from each batch, results were expressed in millimeter.

Weight variation test:

Twenty tablets were selected at random, individually weighed in a single pan electronic balance and the average weight was calculated. The uniformity of weight was calculated. The uniformity of weight was determined according to I.P. specification. As per U.S.P not more than two of individual weight should deviate from average weight by more than 7.5% and none deviate more than twice that percentage.

Friability test:

It was done in Roche Friabilator apparatus where the tablets were subjected to the combined effect of abrasion and shock by utilizing a plastic chamber that revolve at 25 rpm dropping the tablets at a distance of six inches with each revolution. Preweighed samples of 20 tablets were placed in the Friabilator, which is then operated for 100 revolutions. The tablets were then dusted and reweighed. Conventional compressed tablets that lose less than 0.5 to 1.0% of their weight are generally considered acceptable.

$$\% F = \{1-(W_t/W)\} \times 100$$

where % F = Friability in percentage

W = Initial weight of tablets

Wt = Weight of tablets after revolution

Dispersibility test[64]

2 tablets were placed in 100 ml of distilled water and stirred until completely dispersed. A smooth dispersion is produced, which passes through a sieve screen with a nominal mesh aperture of ASTM # 22.

Disintegration test[65]

One tablet was kept in each tube of the disintegration apparatus, suspended the assembly in the beaker containing water and operated with the discs for 4 minutes, unless otherwise stated in the individual monograph. Remove the assembly from the liquid.

Dispersible tablet should complete the disintegration within 3 minutes in water (temperature 15°C to 25ºC).

Dissolution studies

In vitro dissolution test

Dissolution studies of all tablets were performed using dissolution tester (Paddle type, TDL-08L, Electrolab, India). Tablets were added to the 900 ml of 0.1 N HCl at 37°C ± 0.5°C, which was stirred with a rotating paddle at 75 rpm. At time intervals of 15 minutes, 1ml samples were withdrawn and equal volume of fresh medium prewarmed at the same temperature was replaced in to the dissolution medium after each sampling to maintain its constant volume throughout the test. Assay carried out using U.V. spectrophotometer (UV 1700 shimadzu /Visible double beam spectrophotometer, Japan) at 272nm.

Details of dissolution test:

- Dissolution test apparatus : USP II (Paddle)
- Speed : 75 rpm
- Volume of medium : 900 ml
- Time interval : 5,10,15,20,25,30,35,40
- Medium used : 0.1 N HCl
- Temperature : 37 ± 0.5 ^{0}C

Assay of tablets (HPLC Method)[35,36,13,45]

Diluent solution

13.6gm of monobasic potassium phosphate was dissolved in 2000ml of water and adjust to pH 5.0 ± 0.1 with 45% (w/w) solution of KOH.

Preparation of standard solution

115mg of amoxicillin trihydrate WS (working standard) was weighed accurately and transfer to 100 ml volumetric flask, 80ml diluent was added and sonicated at room temperature to dissolve the sample and was diluted to the volume with the diluent. The diluent was filtered through 0.45µ nylon membrane filter, discarding first few ml of filtrate.

Sample preparation

5 tablets were weighed and noted, then transferred in to 500ml volumetric flask and 350ml of diluent were sonicated for 5 min and diluent was made up to the mark and a magnetic stirring bar was placed and stirred for 30 min. The content was filtered and made up to 25ml.

Procedure

Inject the above solutions as per the following sequence

Table No.8

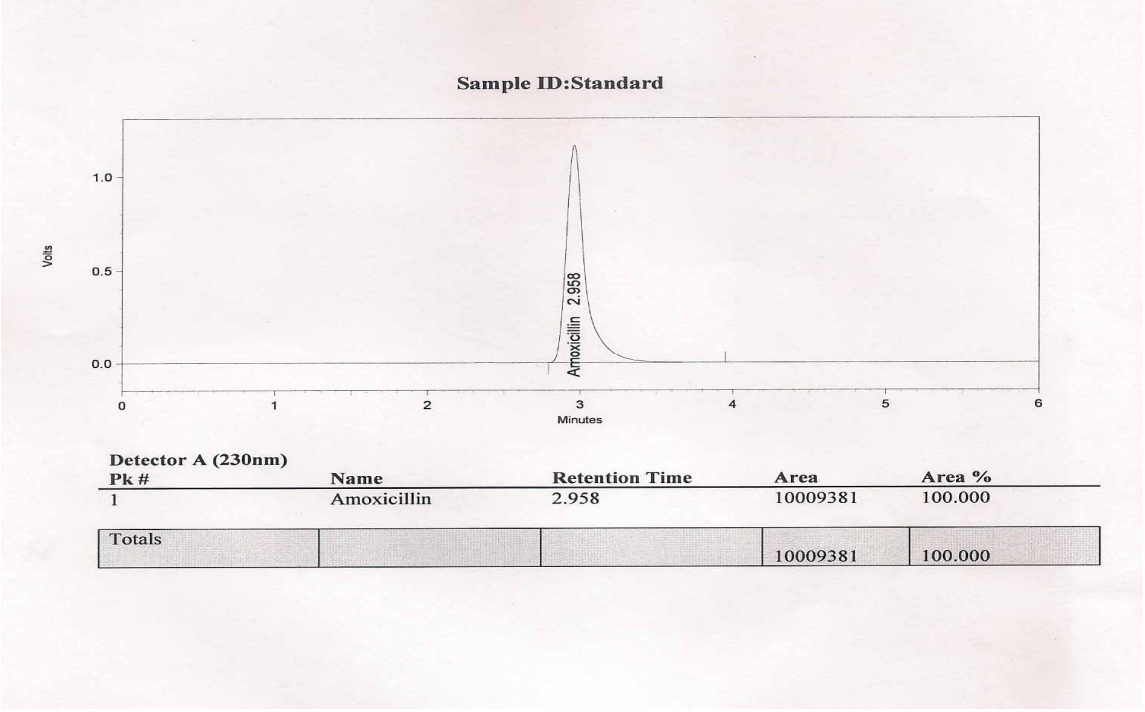
Injection solution	No of injection	Interpretation/calculate
Standard	5	To calculate the % RSD
Test solution a1	1	To calculate % of assay
Test solution a2	1	To calculate % of assay

Calculation

Percentage amount of amoxicillin trihydrate

$$= \frac{\text{sample area} \times \text{standard weight} \times 500 \times 25 \times (\text{purity of std}) \times (100\text{-w}) \times \text{avg. wt}}{\text{standard area} \times 100 \times \text{sample weight} \times 10 \times 100 \times 100}$$

STANDARD CURVE OF HPLC METHOD



Detector A (230nm)

Pk #	Name	Retention Time	Area	Area %
1	Amoxicillin	2.958	10009381	100.000
Totals			10009381	100.000

DIFFERENTIAL THERMAL ANALYSIS (DTA)[71-76,80]

Thermal analysis comprises a group of technique where the properties of the material are studied as they change with the temperature. To determine the thermo-physical properties several methods are commonly used differential thermal analysis (DTA), differential scanning analysis (DSC), dilatometry (DIL), evolved gas analysis (EGA) etc. in pharmacy the main application of the DTA is used for the studying the phase transition under different atmospheric influence, temperature and heating1. DTA is a method for determining the temperature of the phase transition like melting point, solidification onset, re-crystallization onset etc. Analytical work in the area of TGA included compositional analysis of drugs, the volatile components of substance, effects of water vapor on the stability of crystalline drugs and excipients. The purpose of this study was to examine the thermal stability of the optimized formulation by the combined use of DTA and TGA.

The DTA analysis was carried out to identify the compatibility between the drug and the excipients. The DSC analysis of the optimized formulation and Pure drug were carried out using ASTM E-537-98, TA instruments Inc. Samples were weighed and heated in a platinum cups with the reference material calcined alumina at rate of 10°C between 30°C to 600°C under the nitrogen atmosphere.

X-RAY DIFFRACTION STUDIES[83-85,87,88]

The interaction of the drug and excipients were determined by the X-ray diffractometer under the following condition: target/filter (monochromator) Cu, voltage 40 Kv, current 30mA, receiving slit 0.2 inches. The data were collected in the continue scan mode. The scanned range was 0 to 80°.

STABILITY STUDIES[46,79,82,90-92]

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, and to establish a re-test period for the drug substance or a shelf life for the drug product and recommended storage conditions.

The choice of test conditions defined in ICH guideline is based on an analysis of the effects of climatic conditions in the three regions of the European countries, Asian and the United States. The mean kinetic temperature in any part of the world can be derived from climatic data, and the world can be divided into four climatic zones, I-IV. This guideline addresses climatic zones I and II. The principle has been established that stability information generated in any one of the three regions of the European countries, Japan and the United States would be mutually acceptable to the other two regions, provided the information is consistent with this guideline and the labeling is in accord with national/regional requirements. The stability studies conducted in this work are mainly based on the ICH guide lines.

The stability studies were conducted by storing the tablet in a stability chamber at 30ºC / 65% RH and 40ºC / 75% RH for three months, the tablet physical properties and dissolution were examined once in a month. Each tablet were wrapped in an aluminum foil and packed in black PVC bottle and stored for three month. After one month tablets, were analyzed for its physical properties and dissolution properties.

ANALYSIS OF RELEASE DATA[93,6]

To analyze the mechanism of release, the best formulation was subjected to some statistical tests. The release data obtained were treated according to zero-order (cumulative amount of drug release versus time), first-order (log cumulative percentage of drug remaining versus time), Higuchi (cumulative percentage of release versus square root of time) and Korsmeyer-Peppas (log cumulative percentage of drug released versus time) equation models.

7. PRODUCTION COST COMPARISON

Comparison of production cost of Marketed formulation Vs optimized formulation

The optimized formulation price has been compared with the innovator formulation in the production cost, which has been found out that the optimized formulation has less production cost, the economical value of the dosage form has decreased and found to be a successful formulation. The below table shows the results.

Table No.9

Ingredients	**Price/kg**	**Dosage form price/10 tablet**	**Ingredients**	**Price/kg**	**Dosage form price/10 tablet**
Amoxicillin trihydrate(Work)	1500	4.37	Amoxicillin trihydrate(Marketed formulation)	2000	5.84
Crospovidone	350		Crospovidone	350	
Croscarmellose	400				
Magnesium stearate	100		Magnesium Stearate	100	
Colloidal silicon	90		Colloidal silicon	90	

8. RESULT AND DISCUSSION

U V absorption spectra of Amoxicillin trihydrate

Amoxicillin trihydrate was dissolved in a suitable solvent and it was scanned at a wavelength 200nm-400nm were 0.1N HCL as a blank, using double beam UV/Visible spectrophotometer. The maximum wavelength is found to be 272nm.

FTIR of pure Amoxicillin trihydrate

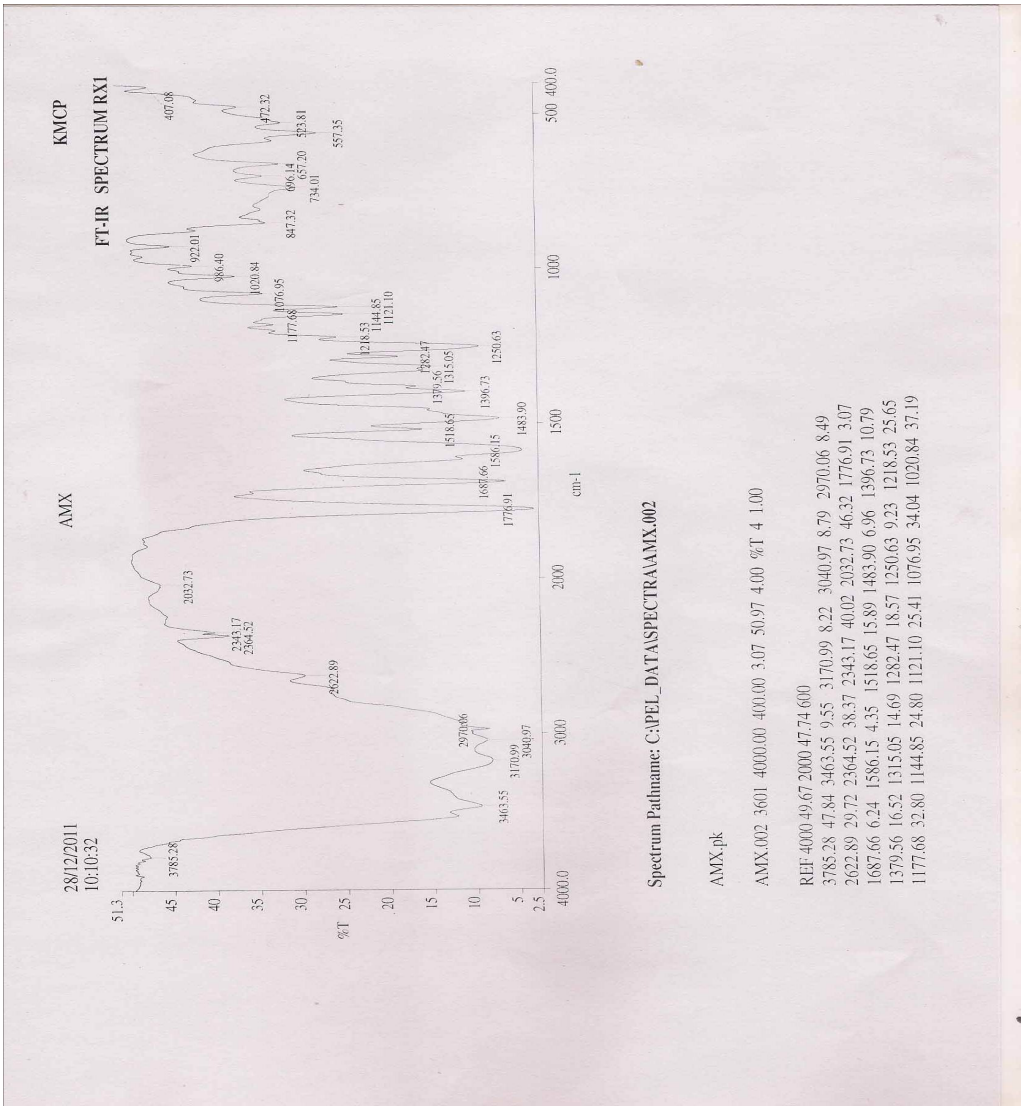


Figure 2

Drug Excipients compatibility study: Interaction of the drug with excipients was determined using FT-IR spectral analysis; these studies were mainly carried out to study the chemical interaction of the drug and excipients used in the formulation. Combination of the drug and excipients can cause changes in the chemical consistution of the drug. The samples were taken for FT-IR study.

FTIR of Crospovidone

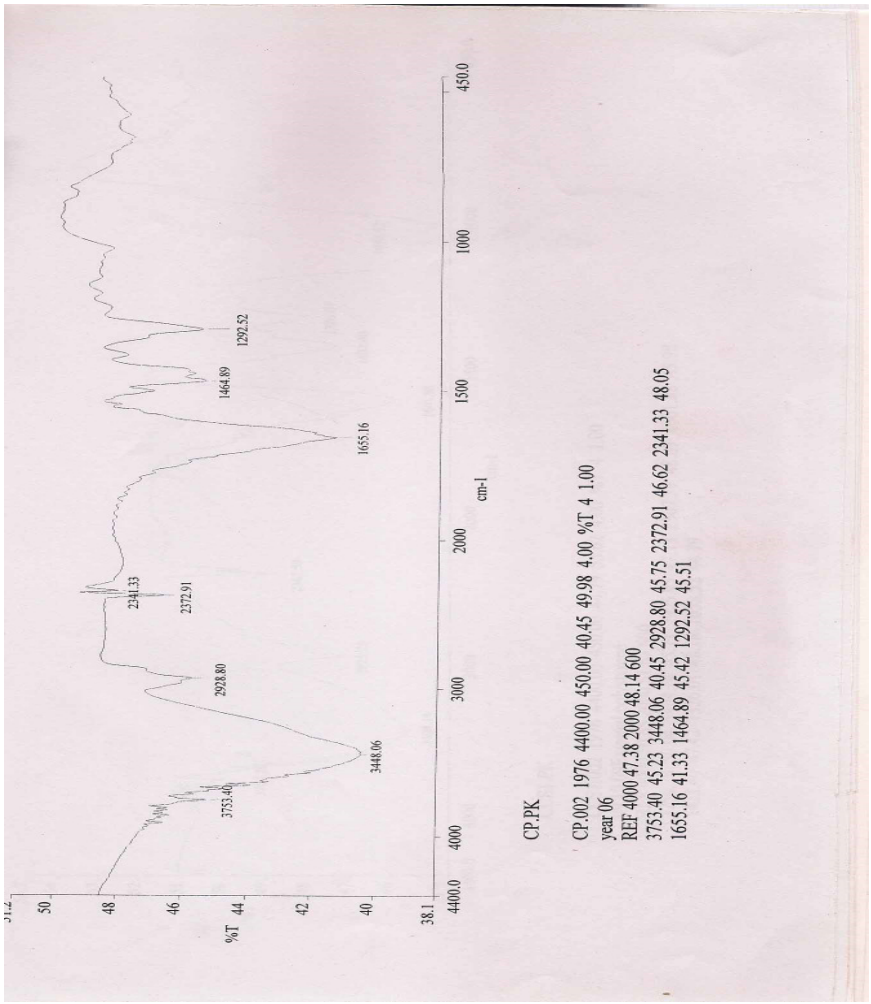


Figure 3

FTIR of Croscarmellose

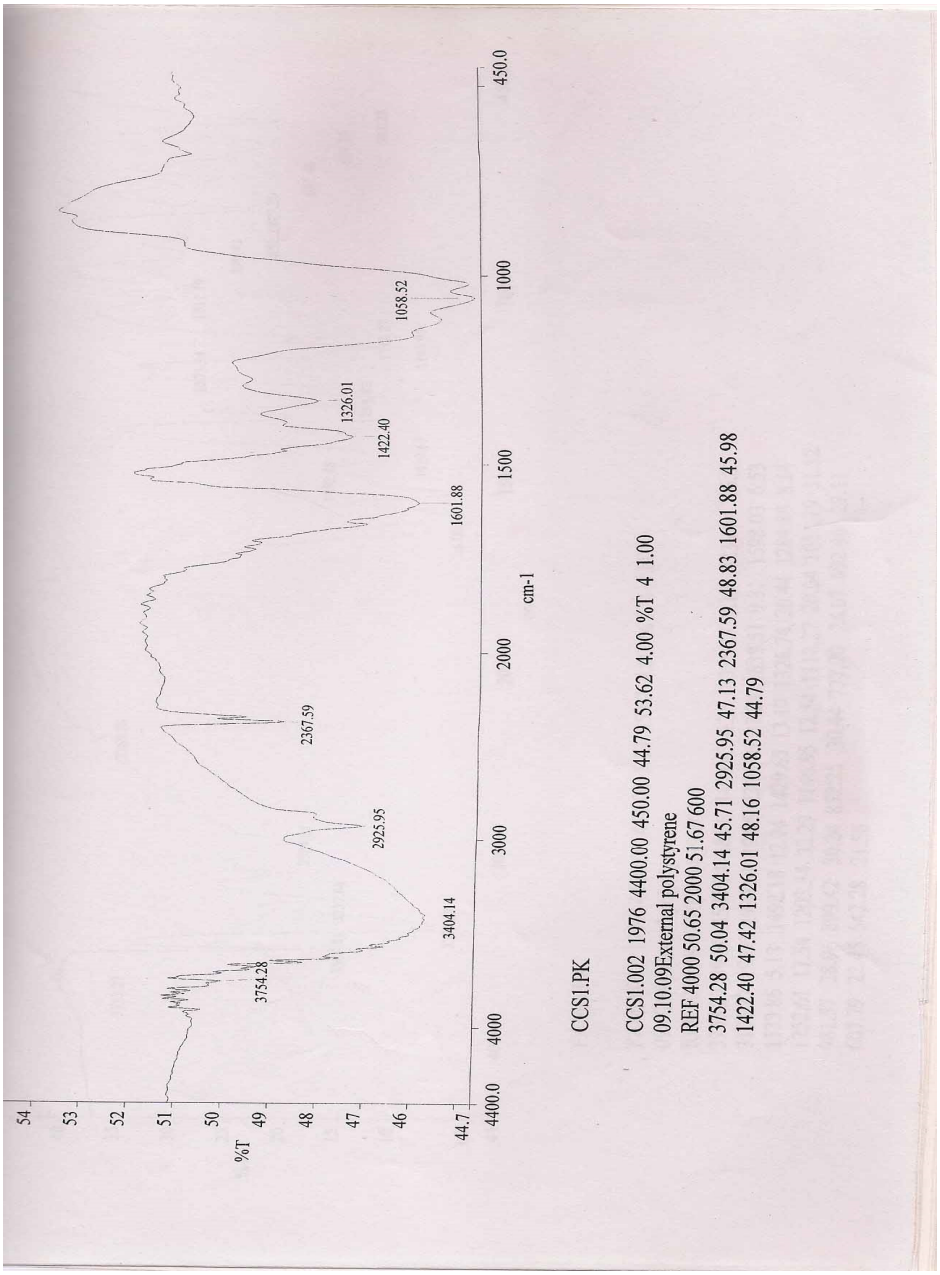


Figure 4

FTIR of Amoxicillin + Crospovidone

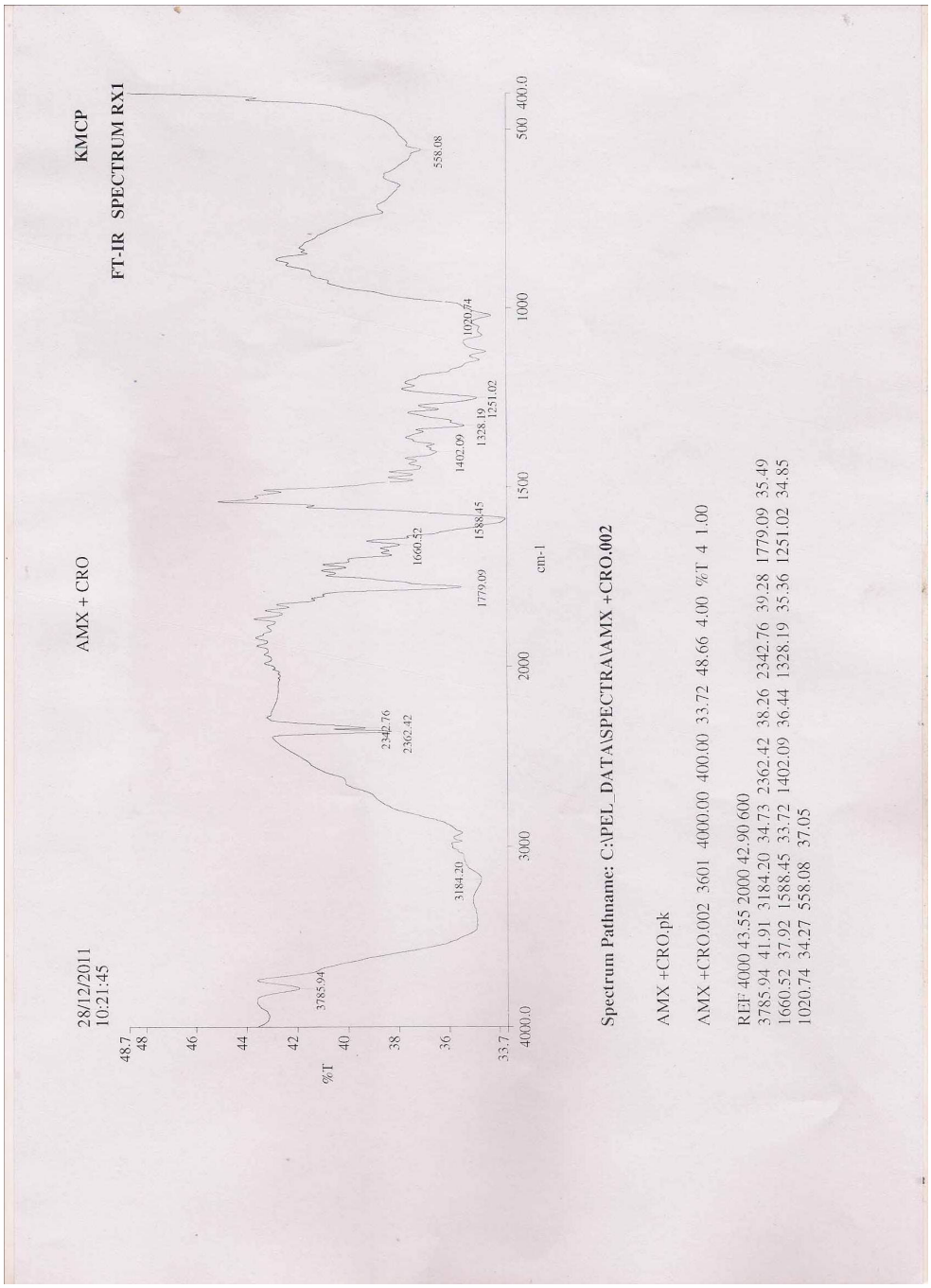


Figure 5

FTIR of Amoxicillin + Croscarmellose

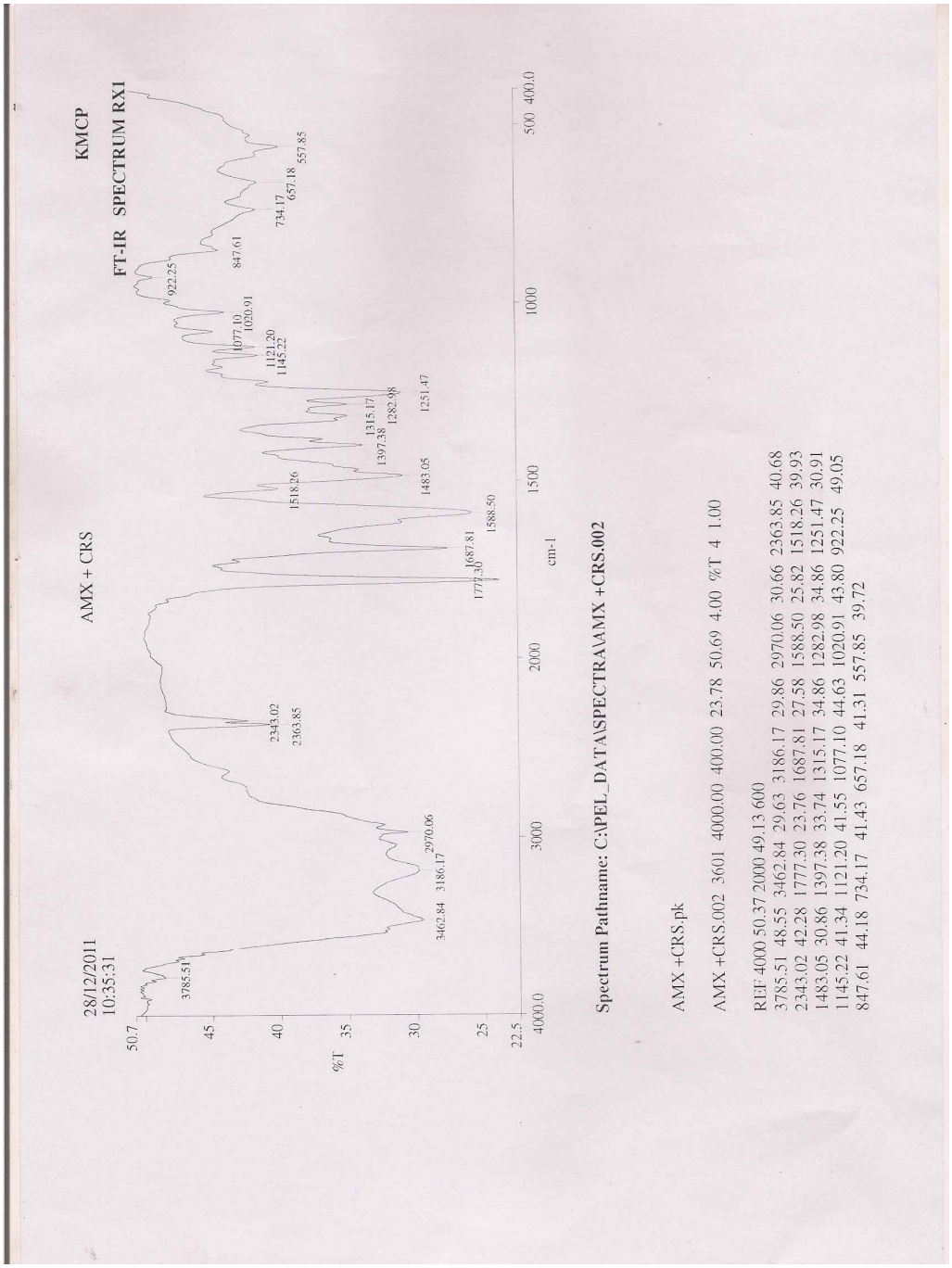


Figure 6

INTERPRETATION OF IR SPECTRUM

FTIR Spectra of pure Amoxicillin trihydrate

Table No. 10

Frequency (cm^{-1})	Groups Assigned	Frequency (cm^{-1})	Groups Assigned
3040.97	C-H Aromatic stretching	657.20	C-S stretching
3463.55	O-H Alcoholic stretching	2970.06	OH carboxylic acid
1121.10	C-N stretching	1776.91	C=O stretching
3170.99	N-H Amide stretching	1250.63	C-O stretching
1687.66	C=O Amide stretching	1250.63	C-O stretching

FTIR Spectra of Crospovidone

Table No. 11

Frequency (cm^{-1})	Groups Assigned
3448.06	N-H stretching
2928.80	C-H stretching
1655.16	C=O stretching
1292.52	C-N stretching

FTIR Spectra of Croscarmellose

Table No. 12

Frequency (cm^{-1})	Groups Assigned	Frequency (cm^{-1})	Groups Assigned
3404.14	O-H stretching	1422.40	O-H stretching
2925.95	C-H stretching	1326.01	C-O stretching
1601.88	C=O stretching		

Discussion

When the FTIR spectrum of the amoxicillin trihydrate (pure drug) and the excipients were compared, there were no major interactions showed in the spectrum. So the above results concluded that the amoxicillin trihydrate has no interaction with added excipients.

Preformulation study of pure Drug (Amoxicillin trihydrate)

Table No.13

Sl. No.	Parameters	Result
1	Bulk Density	0.62gm/ml
2	Tapped Density	0.72gm/ml
3	Angle of Repose	29.16
4	Carr's Index	13.88
5	Hausner Ratio	1.16

Preformulation study of the blend

Table No.14

Batch Code	Bulk Density ± SD	Tapped Density ± SD	Angle of repose ±SD	% Compressibility ±SD	Hausner Ratio ± SD
F1	0.53±0.124	0.67±0.024	30.00±2.55	17.91±0.834	1.21±0.016
F2	0.51±0.0124	0.61±0.0192	29.28±2.60	14.71±1.36	1.17±0.021
F3	0.53±0.0126	0.64±0.0081	35.02±2.55	17.18±1.51	1.20±0.014
F4	0.54±0.0124	0.64±0.0192	34.12±2.26	15.62±0.83	1.18±0.016
F5	0.55±0.0126	0.63±0.024	28.17±2.60	12.69±1.36	1.14±0.021
F6	0.52±0.0124	0.62±0.0192	29.15±2.55	16.12±1.51	1.19±0.016
F7	0.55±0.0126	0.66±0.024	32.15±2.26	16.66±0.83	1.20±0.014
F8	0.51±0.0124	0.61±0.0192	36.21±2.60	16.39±1.36	1.19±0.021
F9	0.53±0.0124	0.62±0.0081	34.12±2.55	14.51±1.36	1.16±0.014
F10	0.54±0.124	0.64±0.024	30.12±2.26	15.62±1.51	1.18±0.014

Discussion

- Amoxicillin trihydrate in powder form were investigated for various physical parameters. The result revealed that it has better flow property, bulk density, tapped density and the compressibility and Hausner ratio confirmed its better flow property.

- Amoxicillin trihydrate and excipients in the blend state had evaluated for its preformulation property. Because it has great role in preparation of the tablets. They showed better flow property and compressibility and Hausner ratio had showed its better suitability for the direct compression and wet granulation method.

Evaluation of Amoxicillin trihydrate dispersible tablets

Table No.15

Test	Hardness (N) ±SD	Friability (%) ±SD	Thickness (mm) ±SD	Average weight (mg) ±SD	Disintegration time (sec) ±SD	Drug content (%) ±SD
F1	130±7.84	0.25±0.07	3.61±0.09	319±1.22	132±7.36	98.32±1.15
F2	118±4.69	0.31±0.03	3.68±0.06	322±1.32	150±9.89	97.65±1.44
F3	111±12.97	0.42±0.06	3.46±0.04	319.5±1.24	140±8.63	98.09±1.48
F4	110±7.84	0.21±0.07	3.50±0.06	322±1.22	96±9.89	96.02±1.15
F5	138±4.69	0.35±0.03	3.52±0.09	320±1.24	120±7.36	97.50±1.48
F6	111±7.84	0.21±0.07	3.41±0.06	319±1.32	150±8.63	99.54±1.44
F7	128±4.69	0.35±0.06	3.68±0.09	323±1.22	96±7.36	95.64±1.15
F8	130±12.97	0.25±0.03	3.52±0.04	320±1.24	72±9.89	99.32±1.48
F9	128±7.84	0.32±0.07	3.60±0.09	321±1.32	64±7.36	98.54±1.15
F10	118±4.69	0.31±0.03	3.55±0.06	320±1.24	25±8.63	101.15±1.44

- **Comparison of disintegration time of various formulation**

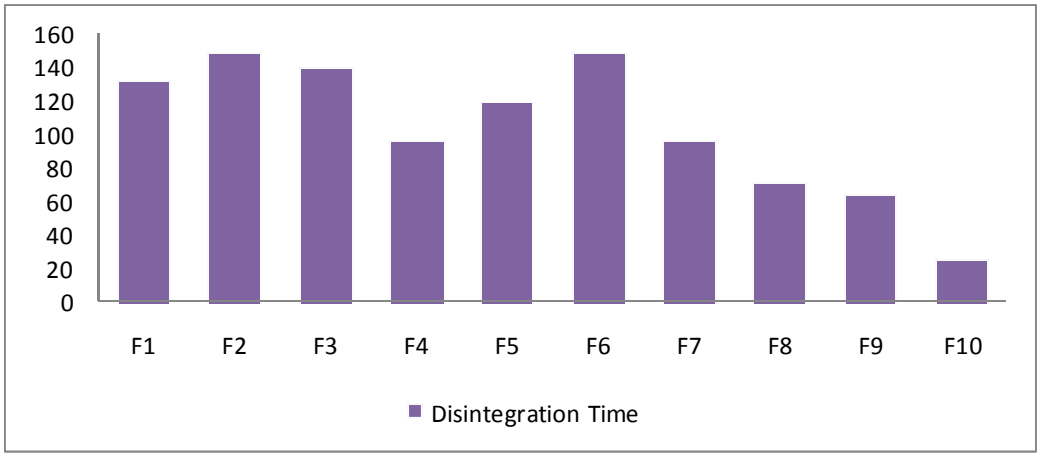


Figure 7

- **Comparison of Assay of various formulations**

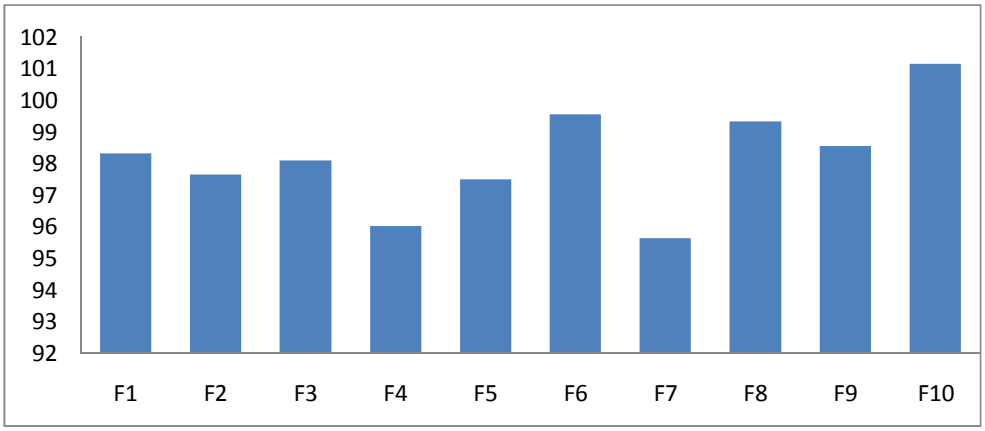


Figure 8

- **Comparison of Disintegration Time of various formulation (seconds)**

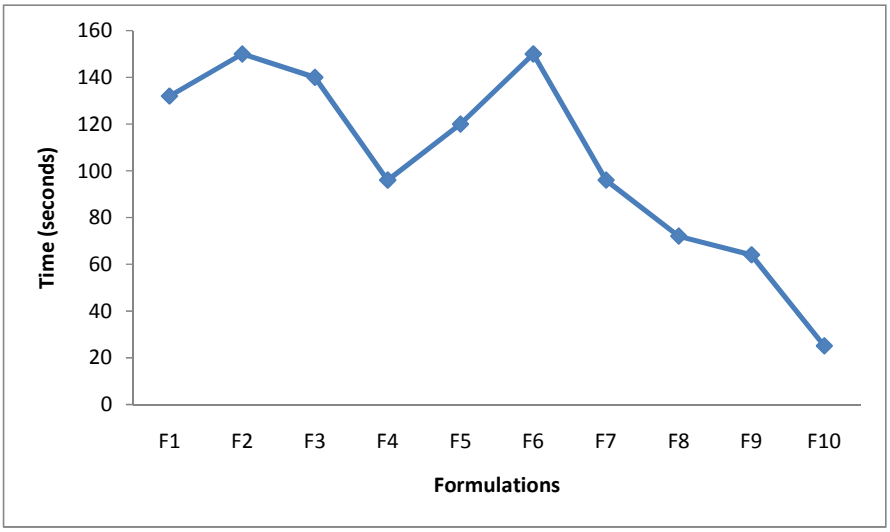


Figure 9

Dissolution profile of Innovator formulation

Table No.16

Sl. No	Time (min)	Amount of drug release	%drug release	Cumulative% release
1	5	30.8	12.32	12.32
2	10	58.2	23.28	23.29
3	15	130.7	52.28	52.30
4	20	185.9	74.36	74.41
5	25	209.6	83.34	83.42
6	30	226.4	90.56	90.65
7	35	235.3	94.12	94.22
8	40	250.8	100.32	100.42

Dissolution Profile of F1

Table No.17

Sl. No	Time (min)	Amount of drug release	%drug release	Cumulative % release
1	5	24.3	9.72	9.72
2	10	51.4	20.54	20.55
3	15	110.6	44.24	44.26
4	20	151.2	60.48	60.52
5	25	170.5	68.20	68.26
6	30	198.9	79.56	79.63
7	35	209.8	83.92	84.00
8	40	221.4	88.5	88.59

Dissolution profile of F2

Table No.18

Sl. No	Time (min)	Amount of drug release	%drug release	Cumulative% release
1	5	20.8	8.32	8.32
2	10	48.6	19.44	19.45
3	15	110.3	44.12	44.14
4	20	160.8	64.32	64.36
5	25	185.4	74.16	74.23
6	30	198.3	79.32	79.40
7	35	204.4	81.76	81.84
8	40	216.0	86.4	86.49

Dissolution profile of F3

Table No.19

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Sl. No	Time (min)	Amount of drug release	%drug release	Cumulative% release
1	5	25.4	10.16	10.16
2	10	51.3	20.52	20.53
3	15	120.6	48.24	48.26
4	20	167.4	66.96	67.01
5	25	190.8	76.36	76.43
6	30	210.8	84.32	84.40
7	35	218.4	87.36	87.45
8	40	225.9	90.36	90.45

Dissolution profile of F4

Table No.20

Sl. No	Time (min)	Amount of drug release	%drug release	Cumulative % release
1	5	18.9	7.56	7.56
2	10	49.5	19.8	19.80
3	15	110.6	44.24	44.26
4	20	143.1	57.24	57.28
5	25	165.6	66.24	66.30
6	30	190.8	76.32	76.39
7	35	208.4	83.36	83.44
8	40	219.6	87.84	87.93

Dissolution profile of F5

Table No.21

Sl. No	Time (min)	Amount of drug release	%drug release	Cumulative % release
1	5	25.4	10.16	10.16
2	10	52.2	20.88	20.89
3	15	101.4	40.56	40.58
4	20	140.8	56.32	56.36
5	25	160.3	64.12	64.18
6	30	186.4	74.56	74.63
7	35	201.6	80.64	80.72
8	40	215.1	86.04	86.12

Dissolution profile of F6

Table No.22

Sl. No	Time (min)	Amount of drug release	%drug release	Cumulative % release
1	5	15.1	6.04	6.04
2	10	30.6	12.24	12.24
3	15	65.4	26.16	26.17
4	20	110.7	44.28	44.30
5	25	120.4	48.16	48.20
6	30	127.8	51.12	51.17
7	35	138.6	55.44	55.49
8	40	149.4	59.7	59.76

Dissolution profile F7

Table No.23

Sl. No	Time (min)	Amount of drug release	%drug release	Cumulative % release
1	5	22.3	8.92	8.92
2	10	54.9	21.96	21.96
3	15	98.4	39.36	39.38
4	20	119.7	47.88	47.92
5	25	130.6	52.24	52.29
6	30	175.5	70.2	70.20
7	35	201.3	80.52	80.59
8	40	221.4	88.56	88.64

Dissolution Profile of F8

Table No.24

Sl. No	Time (min)	Amount of drug release	%drug release	Cumulative% release
1	5	19.7	7.88	7.88
2	10	49.5	19.8	19.8
3	15	99.3	39.72	39.74
4	20	130.3	52.12	52.16
5	25	160.2	64.08	64.13
6	30	180.1	72.04	72.11
7	35	205.4	82.16	82.24
8	40	225.9	90.36	90.45

Dissolution profile of F9

TableNo.25

Sl. No	Time (min)	Amount of drug release	%drug release	Cumulative% release
1	5	22.6	9.04	9.04
2	10	54	21.6	21.61
3	15	95.3	38.12	38.14
4	20	121.5	48.6	48.64
5	25	146.9	58.76	58.81
6	30	166.5	66.6	66.6
7	35	202.4	80.96	81.03
8	40	225.6	90.16	90.24

Dissolution profile of F10

Table No.26

Sl. No.	Time (min)	Amount of drug release	%drug release	Cumulative% release
1	5	28.3	11.32	11.32
2	10	57.6	23.04	23.05
3	15	135.7	54.28	54.30
4	20	198.9	79.56	79.62
5	25	205.2	82.2	82.28
6	30	220.4	88.16	88.25
7	35	230.7	92.28	92.37
8	40	248.8	99.01	99.11

Comparison of % drug release of various formulation.

Cumulative % drug released vs time in min

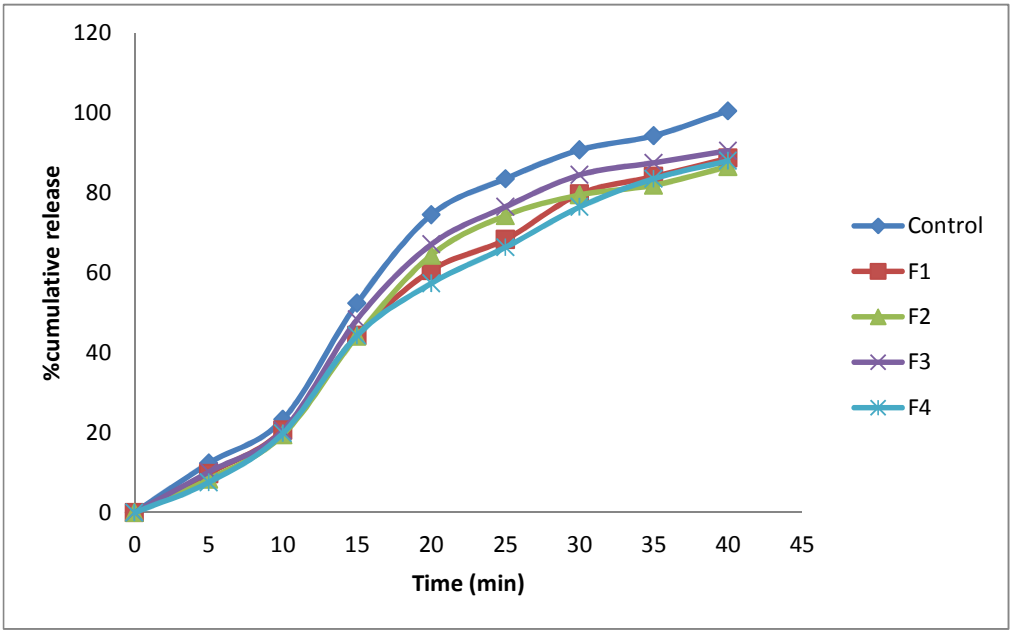


Figure 10

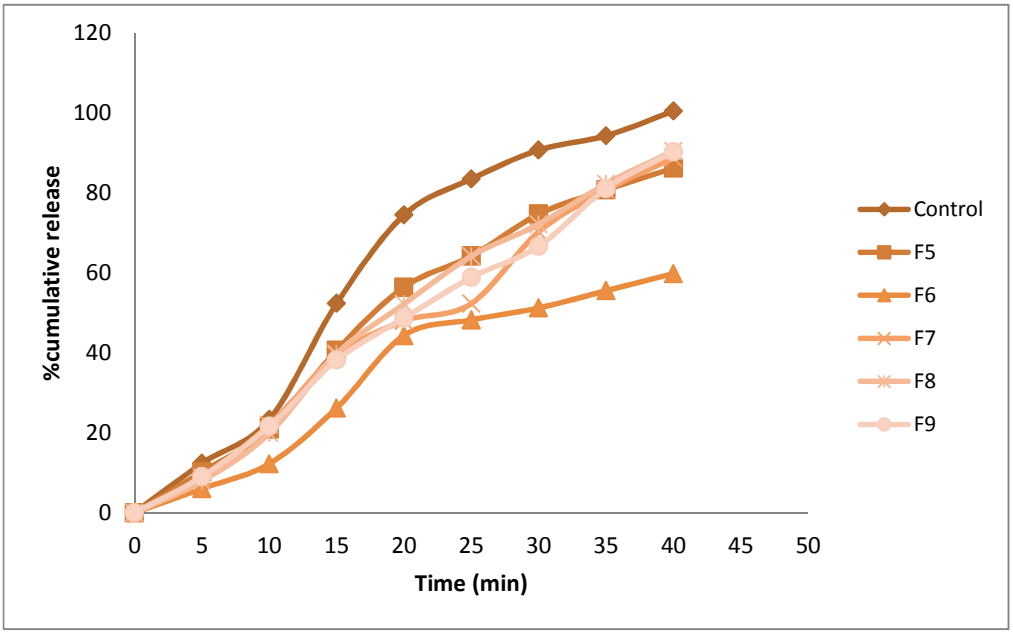


Figure 11

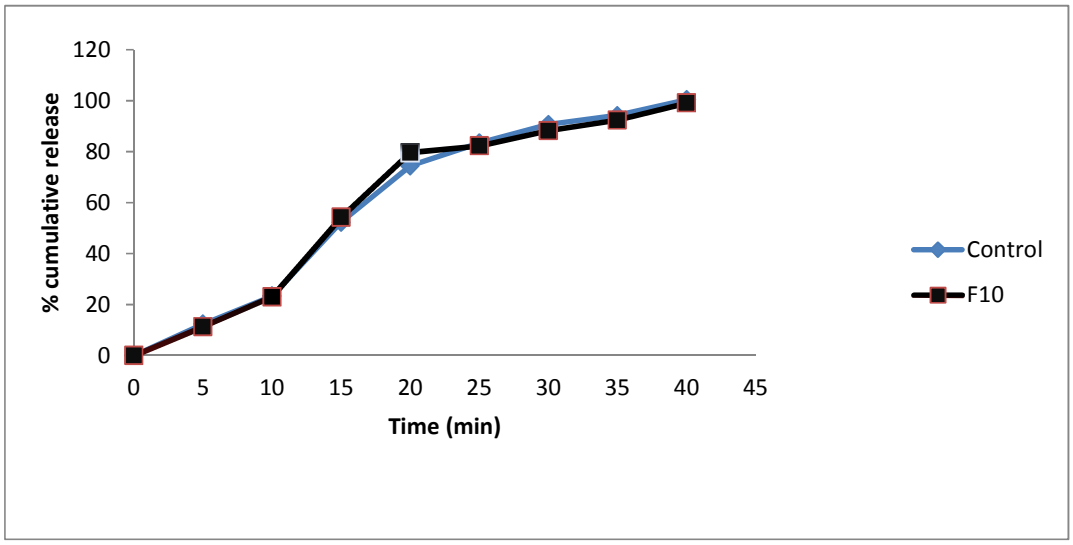
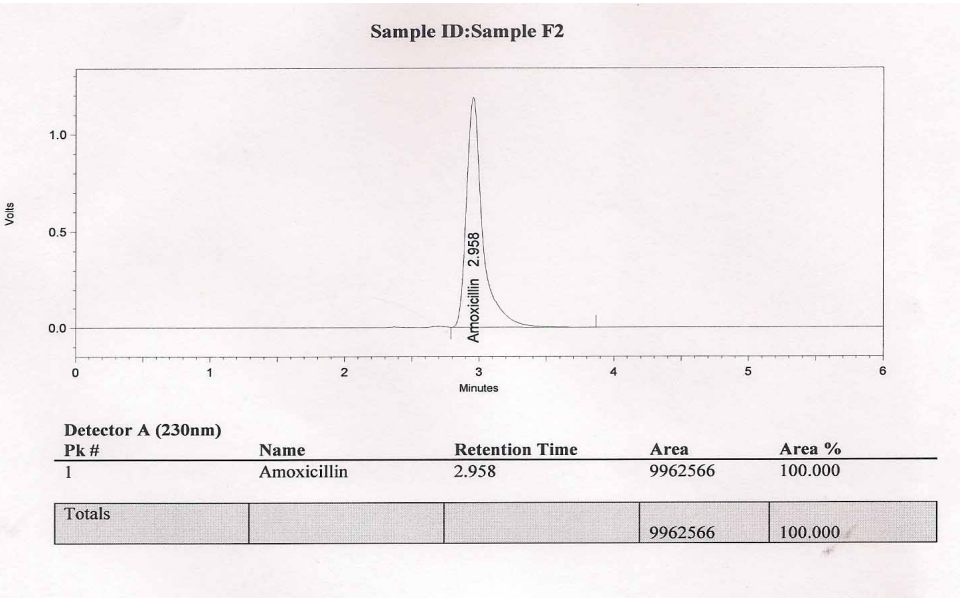

120
100
80
60
40
20
0
% cumulative release
0
5
10
15
20
25
30
35
40
45
Time (min)
Control
F10

Figure12

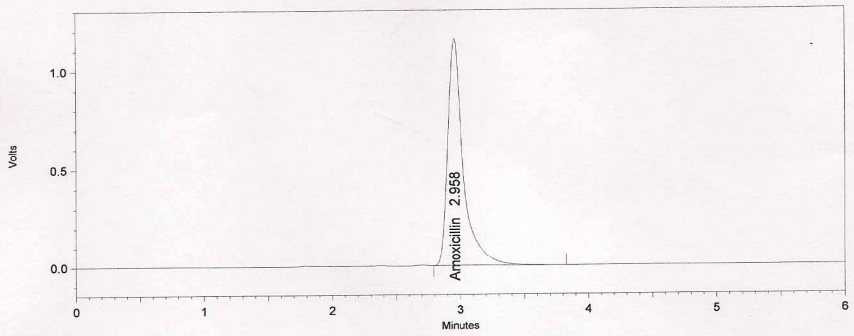
HPLC Chromatogram of formulations (Assay):



Detector A (230nm)

Pk #	Name	Retention Time	Area	Area %
1	Amoxicillin	2.958	9962566	100.000
Totals			9962566	100.000

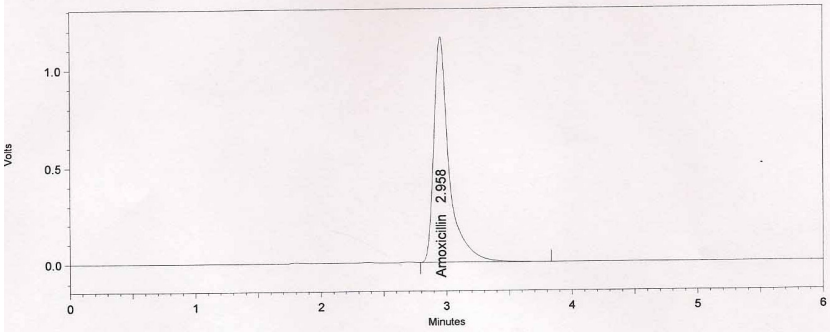
Sample ID:Sample F3



Detector A (230nm)

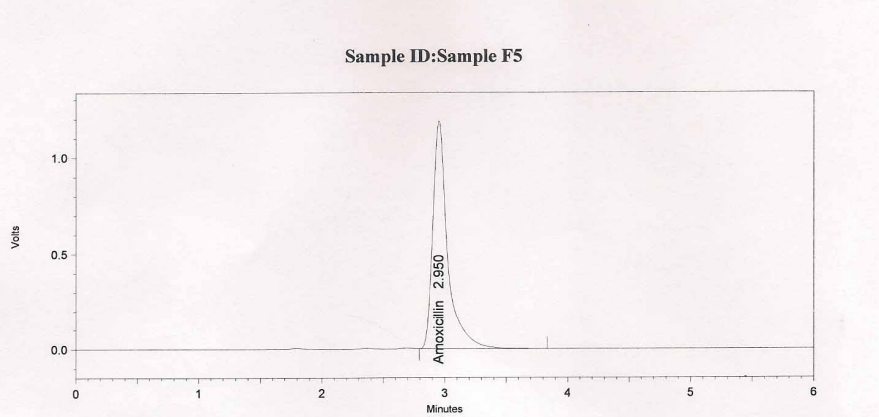
Pk #	Name	Retention Time	Area	Area %
1	Amoxicillin	2.958	9799201	100.000
Totals			9799201	100.000

Sample ID:Sample F4



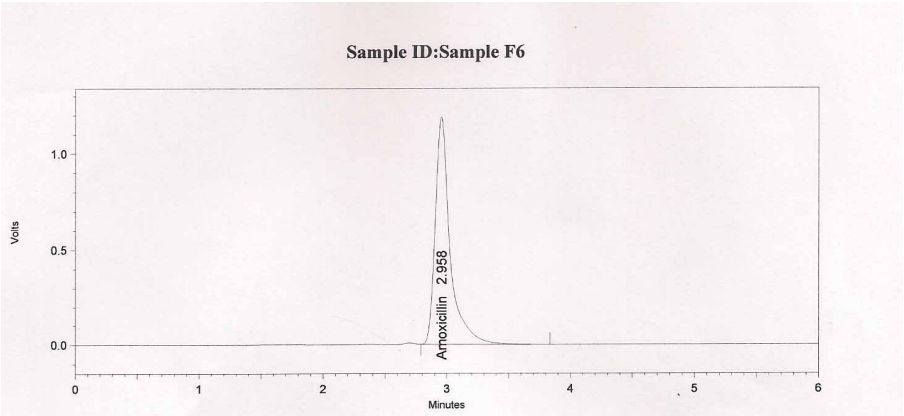
Detector A (230nm)

Pk #	Name	Retention Time	Area	Area %
1	Amoxicillin	2.958	9775307	100.000
Totals			9775307	100.000



Detector A (230nm)

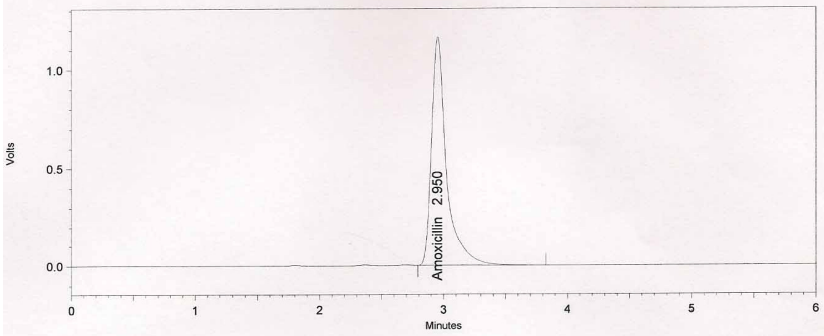
Pk #	Name	Retention Time	Area	Area %
1	Amoxicillin	2.950	9926886	100.000
Totals			9926886	100.000



Detector A (230nm)

Pk #	Name	Retention Time	Area	Area %
1	Amoxicillin	2.958	9914768	100.000
Totals			9914768	100.000

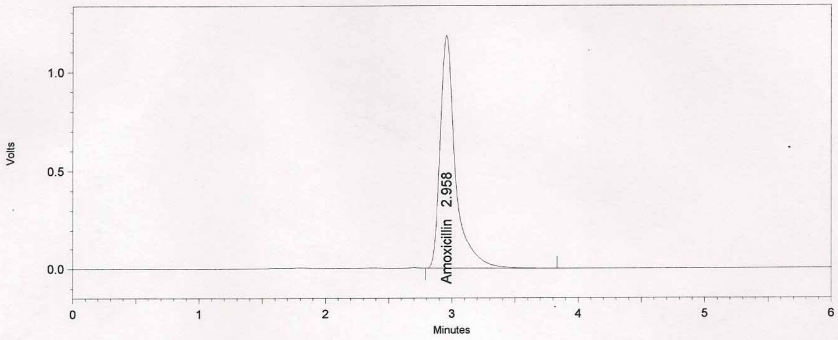
Sample ID:Sample F7



Detector A (230nm)

Pk #	Name	Retention Time	Area	Area %
1	Amoxicillin	2.950	9786323	100.000
Totals			9786323	100.000

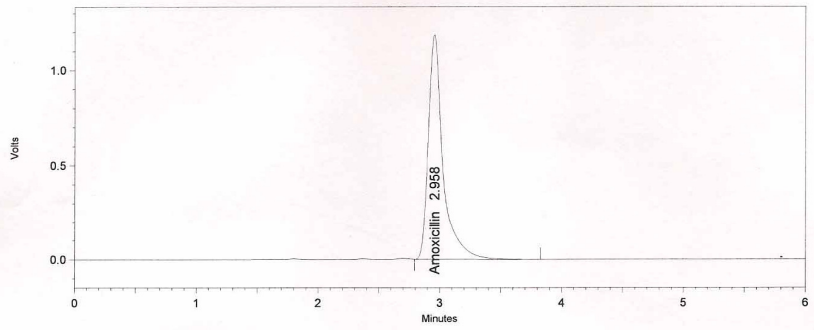
Sample ID:Sample F8



Detector A (230nm)

Pk #	Name	Retention Time	Area	Area %
1	Amoxicillin	2.958	9956034	100.000
Totals			9956034	100.000

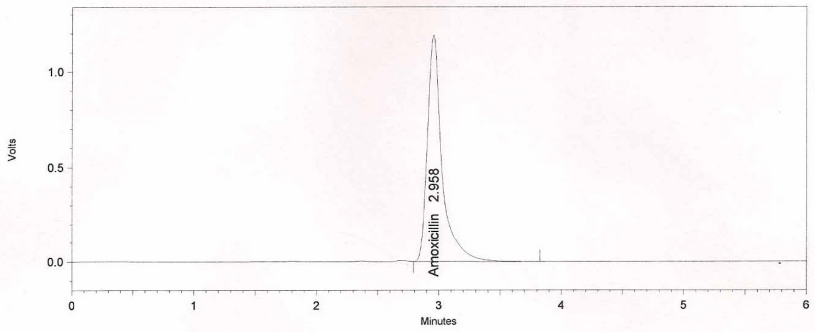
Sample ID:Sample F9



Detector A (230nm)

Pk #	Name	Retention Time	Area	Area %
1	Amoxicillin	2.958	9922438	100.000
Totals			9922438	100.000

Sample ID:Sample F10



Detector A (230nm)

Pk #	Name	Retention Time	Area	Area %
1	Amoxicillin	2.958	9908747	100.000
Totals			9908747	100.000

Discussion

- F1: [with Crospovidone]; The tablet showed very high disintegration time, but shows good hardness and friability and also with minimum deviation in weight and thickness. The releases of the drug from the tablets were below the limits. It also passed the fineness of dispersion.
- F2: [with sodium starch glycolate]; The disintegration time of the tablet is higher than the above formulation. Also showing a good hardness and friability and minimum deviation in the thickness, also the weight variations were within the limits. The release of the drug was poor when compared to the above formulation and it was not within the limits.
- F3 [with Croscarmellose]; In this formulation the addition of the croscarmellose had decreased the disintegration time when comparing to the sodium starch glycolate. Also passed the fineness of dispersion. Shows a better release of the drug from the tablet.
- F4 [with dispersible cellulose]; This formulation was prepared by the wet granulation method, which showed a decreased disintegration time. With a minimum deviation in the parameters. The wet granulation is a time consuming and will cause high production cost. This had resulted in the rejection of the wet granulation in this study and was continued with direct compression method. The release of the drug from the formulation is decreased comparing to the above formulation.

The failure of the single disintegrants to produce good characteristics had resulted in the use of the combination of the disintegrants in the preceding formulations.

- F5 [with maize starch and crospovidone]; They showed an increase in the disintegration time and the release of the drug was below the limits specified. This limitation in the formulation were tried to be overcomed in the next formulation.
- F6 [with maize starch and sodium starch glycolate]; This formulation shows increased disintegration time and the dissolution parameters were below the limits. They passed the dispersion test and other parameters were within the limits.

- F7 [with maize starch and croscarmellose]; Formulation which shows a decreased disintegration time with better hardness. The releases of the drug from the tablet were decreased considering the above formulation. They passed the dispersion test.
- F8 [with maize starch, crospovidone and croscarmellose]; This formulation results better disintegration time and increased drug release when comparing to the above formulations. They also passed the dispersion test.
- F9 [with sodium starch glycolate and croscarmellose]; When compaired to the previous formulations, this formulation showed an decrease in the disintegration time of 64 sec with sufficient thickness and hardness. It also shows increased drug release with minimum deviation in the weight variation. It also passes the dispersion test.

The defects in these formulations are eradicated in the preceding formulation with the replacement of the sodium starch glycolate with crospovidone in the preblending stage.

- **F10 [with crospovidone and croscarmellose];** When compared to the previous formulations the combination of the crospovidone and croscarmellose shows excellent disintegration time of 25 seconds. They also showed good dissolution profile within 40 minutes (99.11). This formulation which shows good characteristic on the evaluation of the tablet. Also passed the dispersion test.

So this formulation showing disintegration of 25 seconds and drug release of 99.11% was found to be excellent dispersible tablet satisfying all the requirements for dispersible tablet has considered as the optimized formulation.

It was later considered for the thermal studies, X ray diffraction studies and evaluated for the stability of the tablet under different conditions.

Discussion

- **Differential Thermal Analysis (DTA)**

The DTA thermogram studies were carried out to determine the thermal compactability of the excipients with the drug in the optimized formulation.

The Tg values of the Amoxicillin trihydrate (pure drug) was 196.22°C

When DTA thermogram for Amoxicillin trihydrate and optimized formulation of amoxicillin trihydrate dispersible tablet were compared, the Tg value of the pure drug was situated within the Tg values of dispersible tablet revealed that there was no interaction between pure drug and excipients used in the formulation.

- **X Ray diffration studies**

The X Ray diffraction studies were carried out to determine the interaction of the amoxicillin trihydrate with the excipients. The X Ray diffraction which shows no interaction of the drug with the excipients.

Stability study

Best formulation in this work was selected for the stability studies. In this study the tablet had undergone through different environmental conditions to evaluate its stability in the different environment. It will explain the stability of the tablet, following condition are maintained in the stability studies:

- 30ºC / 65% RH analyzed at a time interval of 1 month up to 3 months
- 40ºC / 75% RH analyzed at a time interval of 1 month up to 3 months

Stability studies of formulation F10 at temperature 30ºC / 65% RH

Table No.27

Properties	Control	After 1month	After 2 month	After 3 month
Assay (%)	99.15	98.95	98.53	98.20
Disintegration time (min)	0.25	0.28	0.30	0.32
Hardness (N)	118	118	115	114
Friability (%)	0.31	0.31	0.29	0.25

Dissolution profile of F10

Table No.28

Time (min)	Cumulative % Drug Release			
	Control	After1 month	After2 month	After3 month
5	11.32	11.25	11.05	10.94
10	23.05	22.94	22.68	22.34
15	54.30	54.20	53.99	53.78
20	79.62	79.40	79.05	78.88
25	82.28	82.01	81.90	81.62
30	88.25	88.05	87.90	87.65
35	92.37	91.21	90.80	89.05
40	99.11	97.96	96.86	95.01

- **Stability studies of formulation F10 at temperature 40ºC / 75% RH**

Table No.29

Properties	Control	After 1month	After 2 month	After 3 month
Assay (%)	99.15	98.84	98.36	98.14
Disintegration time (min)	0.25	0.30	0.34	0.39
Hardness (N)	118	115	110	104
Friability (%)	0.31	0.29	0.28	0.24

Dissolution profile of F10

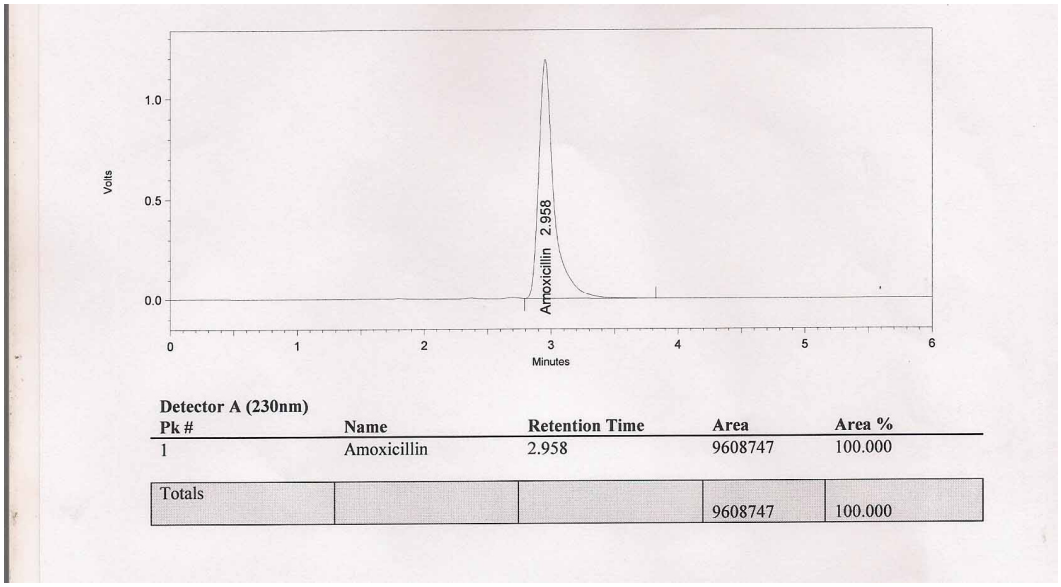
Table No.30

Time (min)		Cumulative % Drug Release		
	Control	After 1 month	After 2 month	After 3 month
5	11.32	11.10	10.95	10.50
10	23.05	22.50	21.85	20.66
15	54.30	53.90	53.40	53.05
20	79.62	78.11	77.72	77.48
25	82.28	81.80	81.58	80.90
30	88.25	87.95	87.65	87.06
35	92.37	91.10	90.80	89.05
40	99.11	97.34	96.26	92.45

HPLC chromatogram of F10 :

- **Stability studies of formulation F10 at temperature 30ºC / 65% RH**

  (After 1 month)

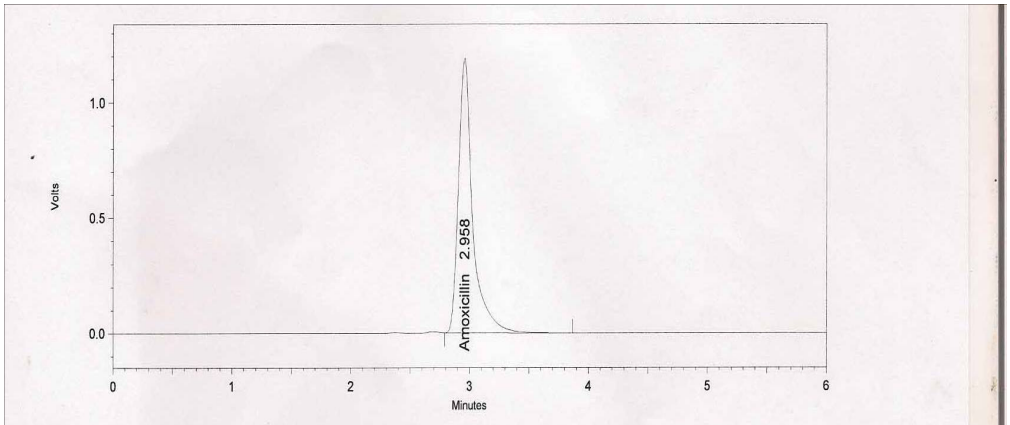


Detector A (230nm)

Pk #	Name	Retention Time	Area	Area %
1	Amoxicillin	2.958	9608747	100.000
Totals			9608747	100.000

- **Stability studies of formulation F10 at temperature 30ºC / 65% RH**

  (After 2 month)

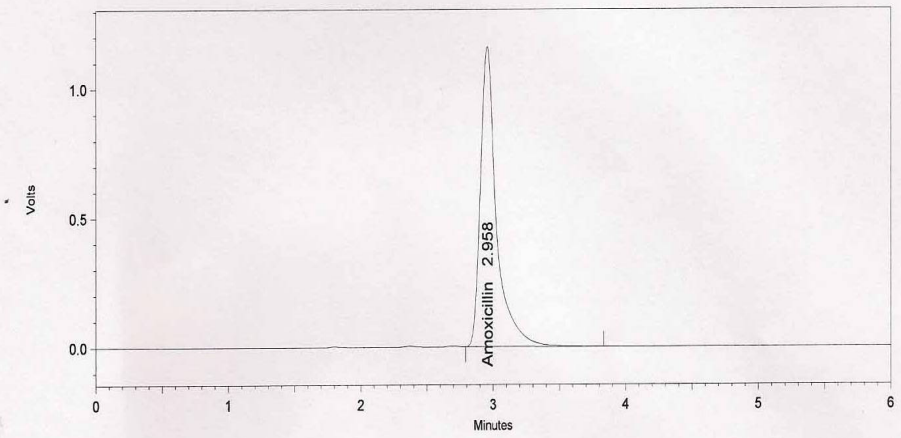


Detector A (230nm)

Pk #	Name	Retention Time	Area	Area %
1	Amoxicillin	2.958	9599201	100.000
Totals			9599201	100.000

- **Stability studies of formulation F10 at temperature 30ºC / 65% RH**

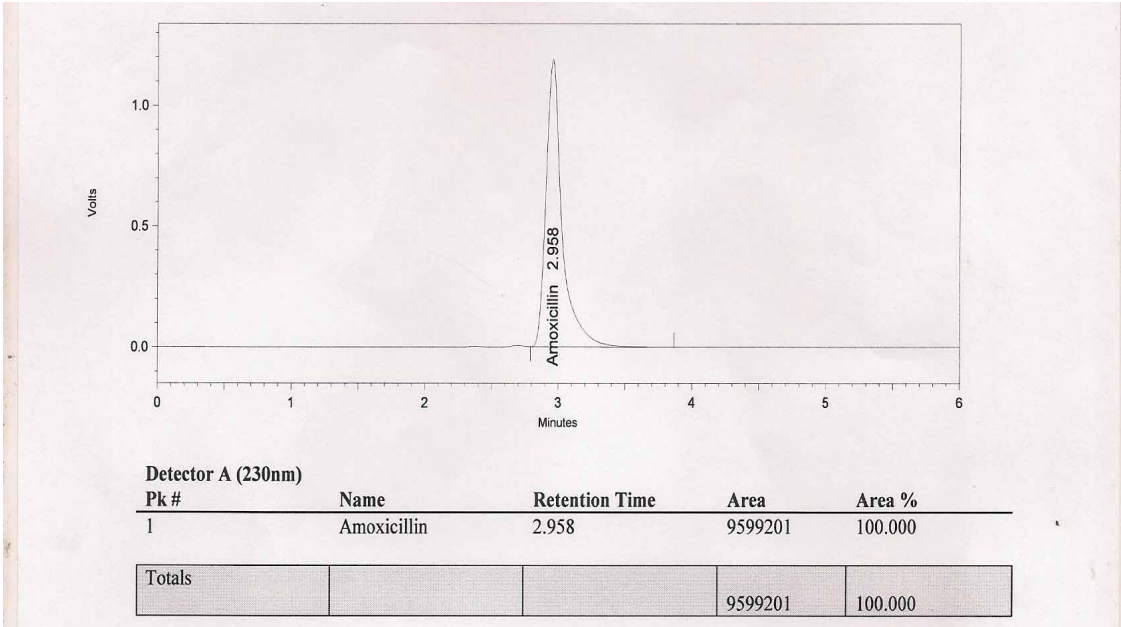
  (After 3 month)



Detector A (230nm)

Pk #	Name	Retention Time	Area	Area %
1	Amoxicillin	2.958	9775307	100.000
Totals			9775307	100.000

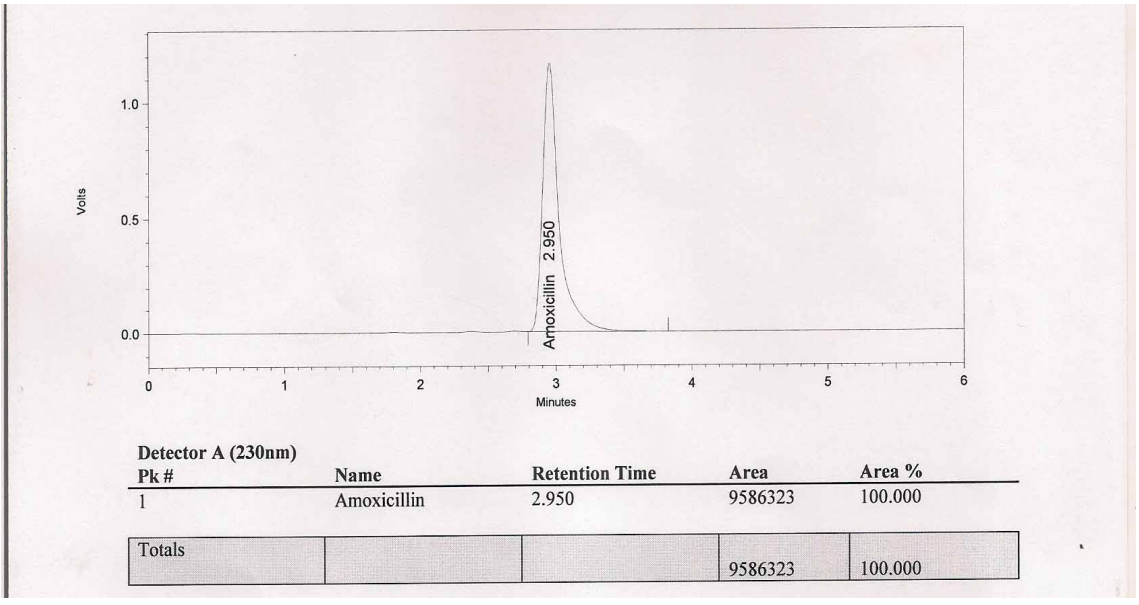
- **Stability studies of formulation F10 at temperature 40ºC / 75% RH (1 month)**



Detector A (230nm)

Pk #	Name	Retention Time	Area	Area %
1	Amoxicillin	2.958	9599201	100.000
Totals			9599201	100.000

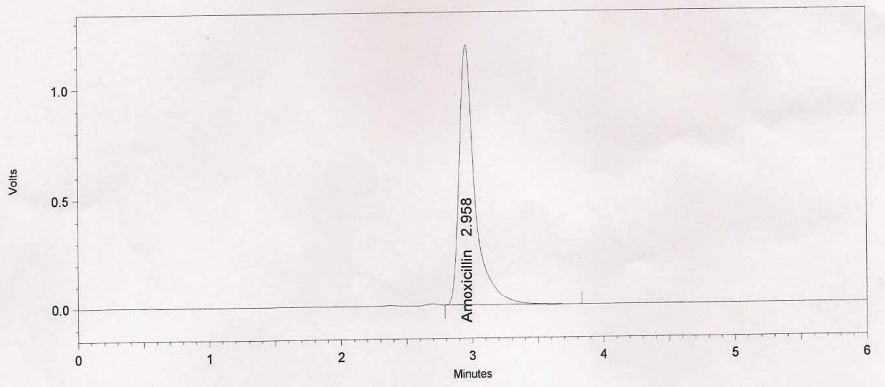
- **Stability studies of formulation F10 at temperature 40ºC / 75% RH (2 month)**



Detector A (230nm)

Pk #	Name	Retention Time	Area	Area %
1	Amoxicillin	2.950	9586323	100.000
Totals			9586323	100.000

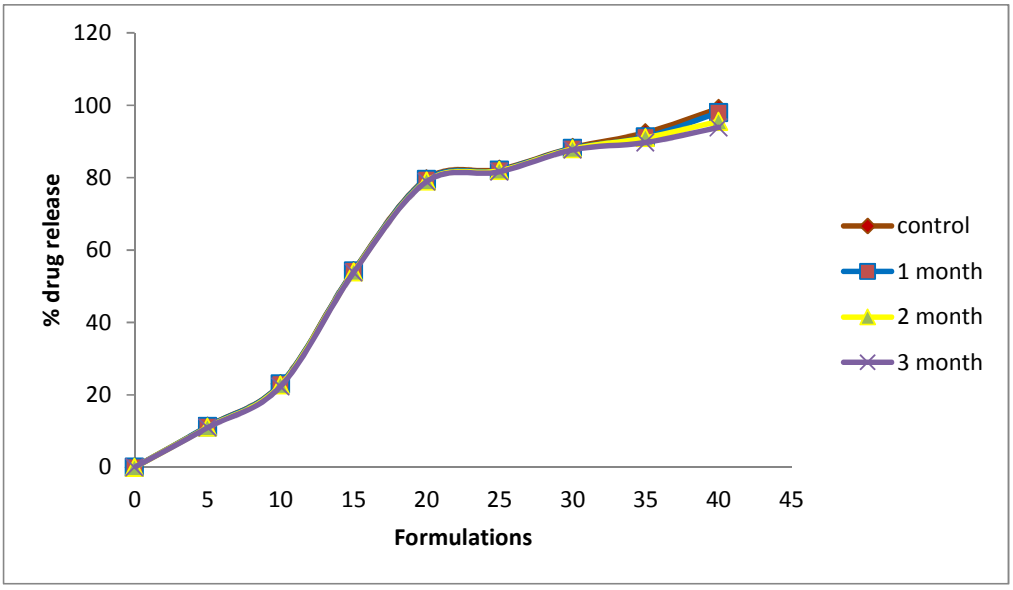
- **Stability studies of formulation F10 at temperature 40ºC / 75% RH (3 month)**



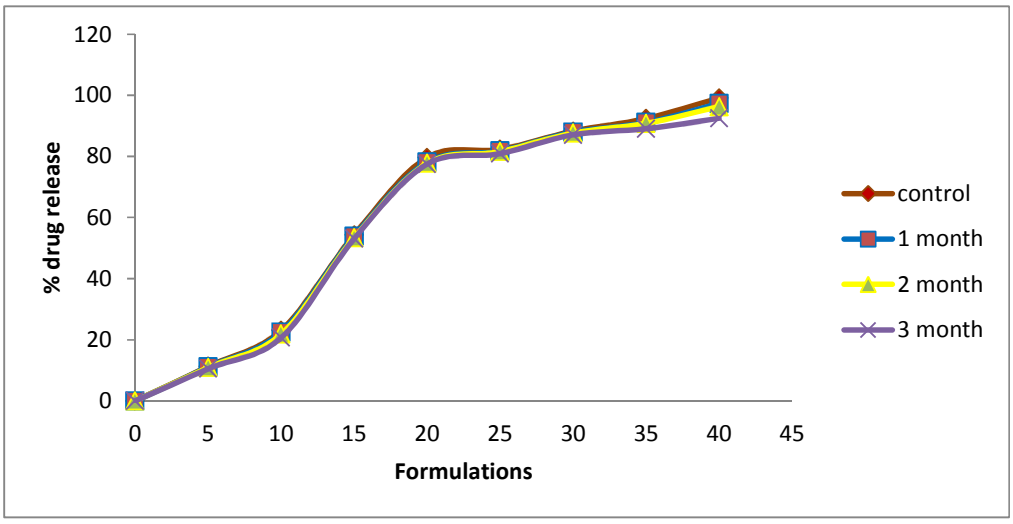
Detector A (230nm)

Pk #	Name	Retention Time	Area	Area %
1	Amoxicillin	2.958	9464768	100.000
Totals			9464768	100.000

Dissolution profile of F10 at 30°C and 65% RH



Dissolution profile of F10 at 40°C and 75% RH

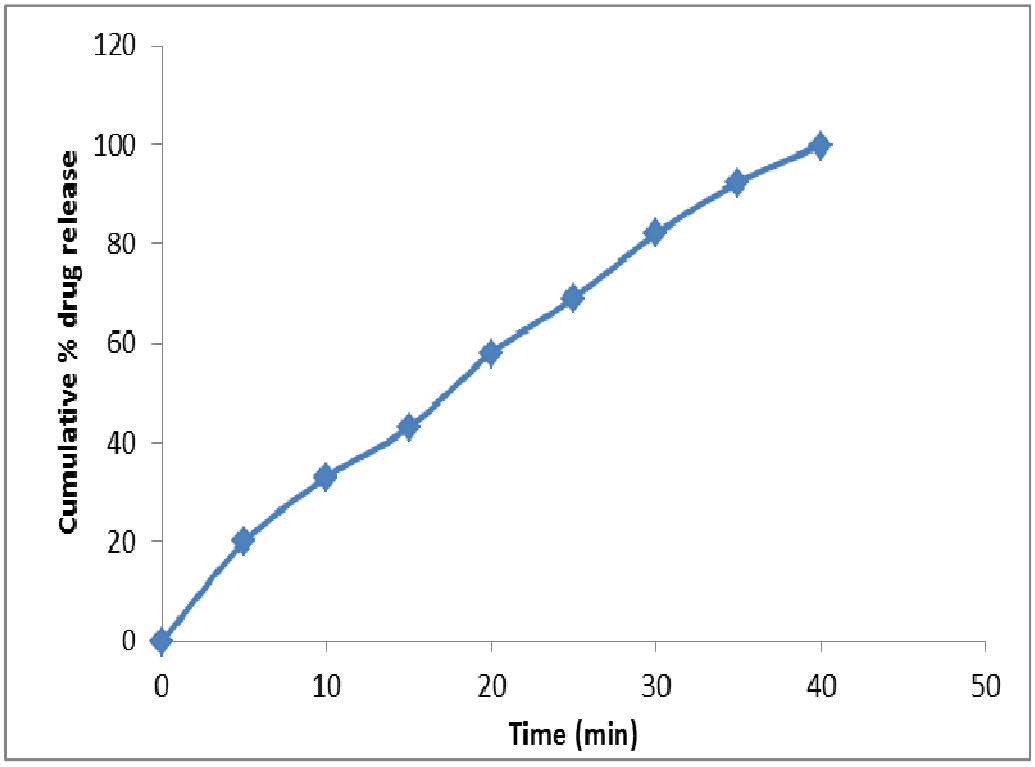


Discussion

The tablets were wrapped in an aluminum foil, packed in black PVC bottles and placed in stability chamber at 30ºc, 65% RH and 40ºc, 75% RH for three month. At the end of each month these tablets were analysed for various tests. When the final and initial results were compared for the stability batch, it was concluded that there was a considerable deviation in the tablet properties. It also shows good disintegration and drug release studies shows no drastic change in the release of drug form the formulation. This concluded that the optimized formulation shows better stability in the above conditions.

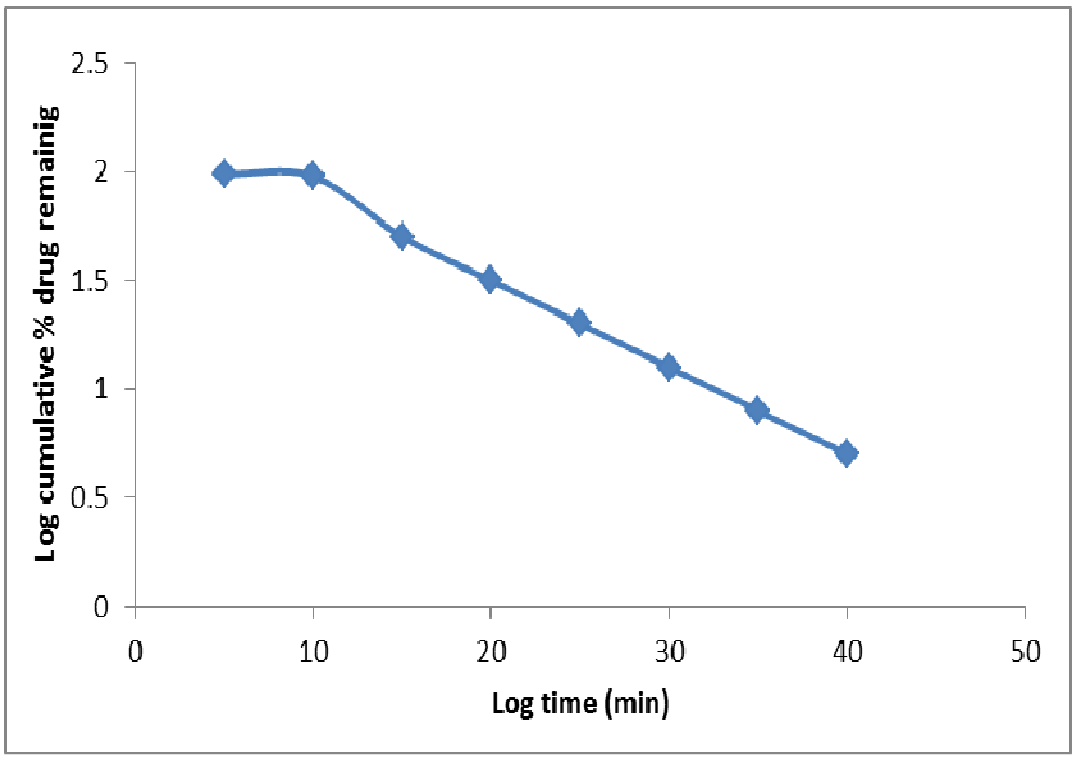
Kinetics of drug release

Zero order release



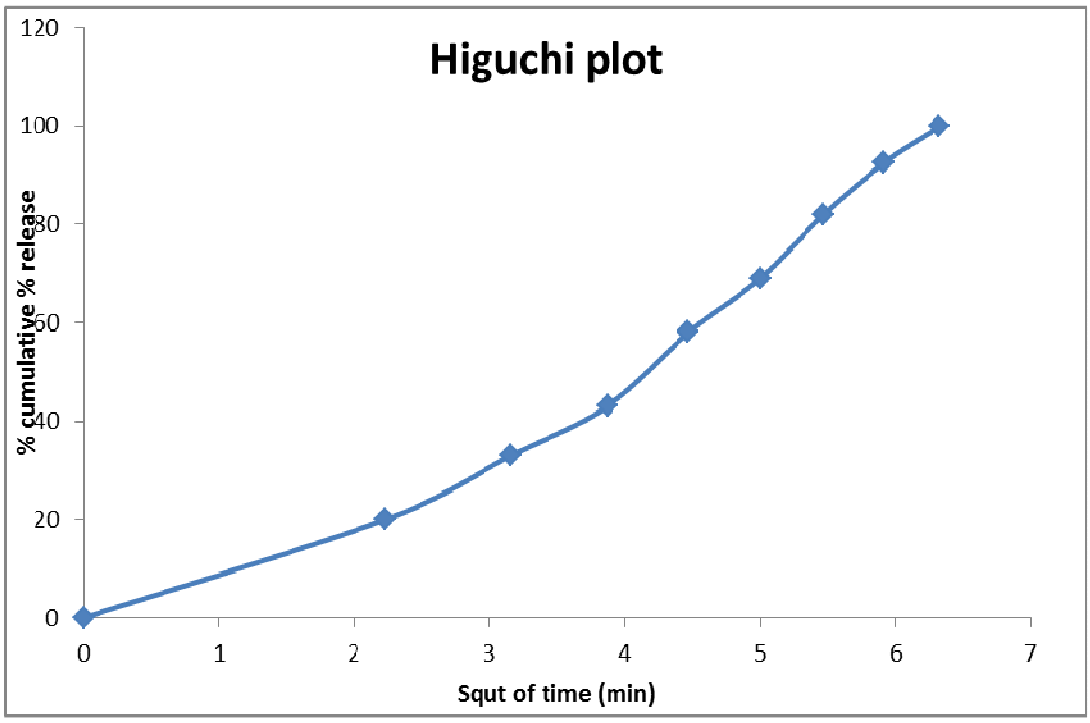
Zero order kinetics
R^2 0.9912

FIRST ORDER RELEASE



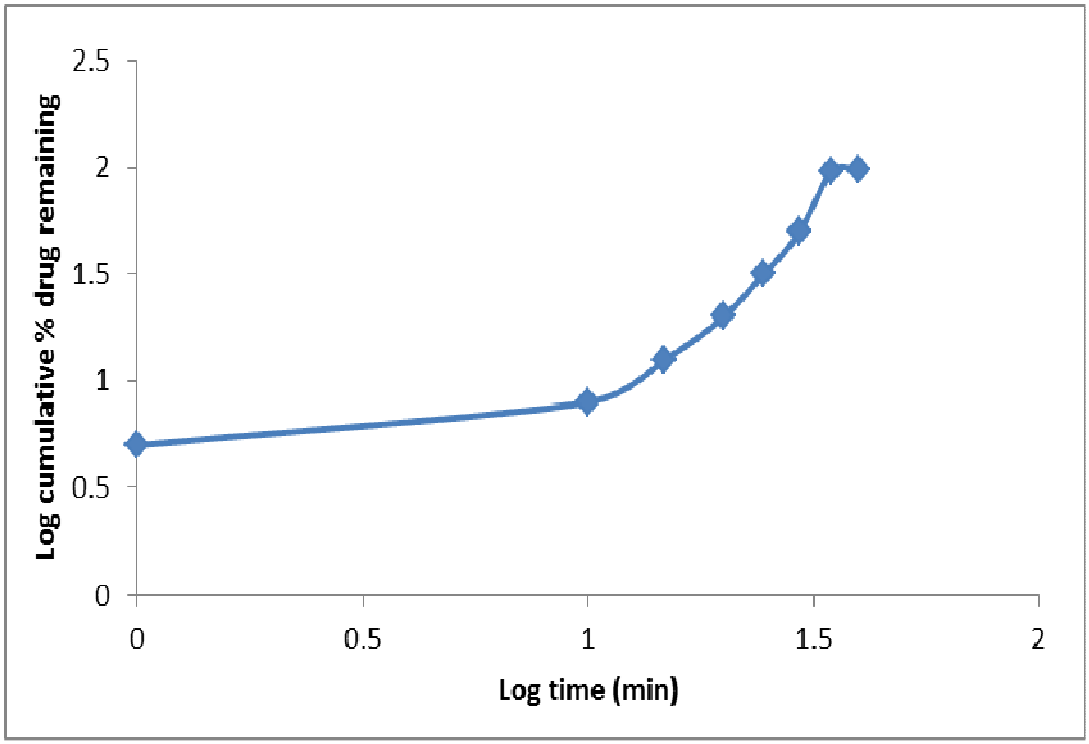
First order kinetics
R^2 0.989

Higuchi Plot



Higuchi release kinetics
R^2 0.953

Korsemeyer – Peppas model Kinetics Plot



Korsemeyer – Peppas
n 0.7118

Discussion

The optimized formulation F10 up on kinetic treatment releases the drug by zero order release kinetics.

A Plot of cumulative % drug release versus time showed linearity. From the plot correlation factor value was found to be 0.9912

9. CONCLUSION

The aim of the present work was to study the effects of different disintegrants on Amoxicillin trihydrate dispersible tablet and to develop a formulation in a low production value, using cheaper raw material but this raw material shows problems in the release of the drug from the formulation. The Amoxicillin trihydrate is formulated with different disintegrants at various amounts in single and in combination. Ten formulations were developed with four disintegrants using direct compression method and wet granulation method. Each formulation composed of drug and disintegrants at various amount. The disintegrants used in this study are maize starch, crospovidone, croscarmellose, sodium starch glycolate etc.

The Preformulation studies and the evaluation studies of the tablet were done and found to be within the limits of the IP. The *In-vitro* drug release studies are conducted and compared with a standard formulation.

The formulation F10 formulated with the combination of Crospovidone and Croscarmellose as disintegrating agents was found to be the optimized formulation. The formulation F10 also exhibited better disintegration time (25 sec) which according to the IP limits is within 3 min. Formulation also shows passes the dispersibility test.

The results of dissolution studies indicated that the formulations F3, F8, F9 and F10, were successful and exhibited drug release pattern very close to innovator drug release profile but the drug release of F10 was found to be better than other formulation i.e. (99.11), also the key factor of a dispersible tablet i.e. disintegration time was found to be much better than any other formulation i.e. (25 seconds). Hence F10 was selected as the optimized formulation.

The Differential Thermal Analysis (DTA) shows that the developed amoxicillin trihydrate dispersible tablet formulation shows better thermal stability. The X Ray diffraction studies also show no interaction of the drug and excipients.

The formulation F10 also passed the test for stability, (30ºc / 65% RH and 40ºc / 75% RH) for three months. The phenomenon of optimized drug release follows Zero order and Korsemeyer-Peppas model.

The above study demonstrated that optimized concentrations of disintegrants and excipients ratios could be successfully employed for formulating amoxicillin trihydrate dispersible tablet. Hence it can be concluded that the above formulation of the amoxicillin trihydrate dispersible tablet shows a better drug release, disintegration time and stability. The production value of this formulation is also lower when compared to other formulations. So the formulation F10 is a successful formulation which has low production and high therapeutic efficacy.

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